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Epidemiology, mathematical modelling and economics of *Streptococcus pneumoniae*: assessing the potential impact of vaccination

by

Alessia Melegaro

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DECLARATION

The work presented in this thesis is the result of original research carried out by the author, Alessia Melegaro, unless otherwise stated. No part of this thesis has been submitted for a degree elsewhere.

Supervision
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Publications arising from this thesis or from work related to this thesis are included in Appendix 1. Where work included in this thesis has been published in joint names, the role of each author is outlined below.

Chapter 3
George R,.**Melegaro A.** Invasive pneumococcal infection England and Wales, 1999. CDR Weekly 2001;11.

R George was the primary author. A Melegaro performed the analysis.

Chapter 4
Melegaro A,.Edmunds WJ. The 23-valent pneumococcal polysaccharide vaccine/Part I – Efficacy of PPV in the elderly: a comparison of meta-analyses. Eur J Epidem 2004;19:353-63.

A Melegaro was the primary author and conducted the meta-analysis. WJ Edmunds supervised the work.

Chapter 5
Melegaro A,.Edmunds WJ. The 23-valent pneumococcal polysaccharide vaccine/Part II – A cost-effectiveness analysis for invasive disease in the elderly in England and Wales. Eur J Epidem 2004;19:365-75.

A Melegaro was the primary author, collected the data, constructed the model and analysed the results. WJ Edmunds supervised the work.

Chapter 6
Melegaro A, Gay NJ, Medley GF. Estimating the transmission parameters of pneumococcal carriage in household. Epidemiol Infect 2004;132:433-41.

A Melegaro was the primary author, constructed the model and analysed the results. N Gay participated in the implementation of the model and supervised the work. GF Medley revised the manuscript and provided advice in relation to the model framework.

Hussain,M; **Melegaro,A**; Pebody,RG; George,R; Edmunds,WJ; Talukda,R; Efstratiou,A; Martin,S; Miller,E. A longitudinal household study of *Streptococcus pneumoniae* nasopharyngeal carriage in a UK setting. Epidemiol Infect 2004 accepted.

M Hussain conducted the study. A Melegaro drafted the manuscript and performed the analysis. R Pebody initiated the study and contributed in finalising the manuscript. R George

provided the data. WJ Edmunds provided advice and revised the manuscript. R Talukda and Martin S performed the laboratory tests and A Esfratiou supervised the laboratory work. E Miller provided the data and supervised the work.

Chapter 9

Melegaro A,.Edmunds WJ. Cost effectiveness analysis of pneumococcal conjugate vaccination in England and Wales. Vaccine 2004; 22; 22(31-32):4203-14.

A Melegaro was the primary author, collected the data, constructed the model and analysed the results. WJ Edmunds supervised the work.

ABSTRACT

This thesis explores aspects of *Streptococcus pneumoniae* (pneumococcus) epidemiology and control, in view of the possible widespread introduction of conjugate vaccines in England and Wales.

A review and analysis of a range of different epidemiological data sources showed that the burden of pneumococcal disease in England and Wales is high and remains mostly a condition of the very young and the elderly. A meta-analysis demonstrated the effectiveness of the polysaccharide vaccine against invasive pneumococcal disease among healthy elderly, to whom vaccination was not recommended at the start of this work. Using this result, a cost-effectiveness analysis assessed the economic acceptability of such a programme, from the public health perspective.

A better understanding of pneumococcal carriage and transmission is required to assess the effectiveness and cost-effectiveness of mass vaccination strategies with the pneumococcal conjugate vaccine. A novel model framework was developed and fitted to a longitudinal dataset of carriage in UK families. The results demonstrated an inverse relationship between duration of carriage and age and highlighted the importance of both family size and composition for persistence in a household. Great dissimilarities were estimated among the specific serotypes in terms of transmissibility, duration of carriage and level of competition. Realistic age-structured dynamic models were developed and used to investigate the impact of a range of vaccine strategies. The importance of serotype replacement, as a consequence of vaccination, was demonstrated. The economic acceptability of alternative interventions with the conjugate vaccine depended on the magnitude of its indirect effects. Herd immunity had a considerable impact on the overall cost-effectiveness of the programmes since it may substantially reduce the burden of disease in older age groups. However, serotype replacement may counterbalance this reduction and lead to a non cost-effective result.

ABBREVIATIONS & ACRONYMS

AOM	Acute otitis media
ARU	Antibiotic Reference Unit
BNF	British National Formulary
CAP	Community-acquired pneumonia
CBA	Cost-benefit analysis
CCS	Case-control study
CDSC	Communicable Disease Surveillance Centre
CEA	Cost-effectiveness analysis
CFR	Case-fatality ratio
CI	Confidence interval
CSF	Cerebrospinal fluid
CPS	Capsular polysaccharide
CUA	Cost-utility analysis
DC	Day care
GP	General Practictioner
HES	Hospital Episode Statistics
HPA	Health Protection Agency
HRG	High risk group
NHRG	Non high-risk group
ICD	International Classification of Disease
ICU	Intensive Care Unit
IPD	Invasive Pneumococcal Disease
JCVI	Joint Committee on Vaccination and Immunisation
LOS	Length of stay
LYG	Life-years gained
MLE	Maximum likelihood estimates
MSGP4	Morbidity Survey of General Practice - Fourth Edition
NGM	Next Generation Matrix
NHS	National Health Service
NOIDS	Notification of Infectious Diseases
NP	Nasopharyngeal
NPA	Nasopharyngal aspirates
NVT	Non-vaccine serotype
OM	Otitis media
ONS	Office for National Statistics
OR	Odds ratio
QALY	Quality adjusted life-years
PCR	Polymerase chain reaction
PCV	Pneumococcal conjugate vaccine
Pnc	Pneumococcal
PP	Pneumococcal pneumonia
PPV	Pneumococcal polysaccharide vaccine
QRCT	Quasi-randomised controlled trial
RCGP	Royal College of General Practitioners
RCT	Randomised controlled trial
RSV	Respiratory Syncytial virus
RSIL	Respiratory and Systemic Infection Laboratory
SAR	Secondary Attack Rate
ST	Serotype
TS	Target serotype
VE	Vaccine efficacy
VT	Vaccine serotype

CHAPTER 1 - INTRODUCTION

Pneumococcal disease is an important public health problem, caused by *Streptococcus pneumoniae*, with the highest incidence of disease observed in the very young and in the elderly. It causes a range of diseases, from mild respiratory tract infection (i.e. sinusitis, otitis media) to more serious invasive or non-invasive conditions (i.e. pneumonia, septicaemia, meningitis). Asymptomatic carriage of *S.pneumoniae* is relatively common, especially in children, with prevalence of carriage decreasing from 50-60% in the first two years of life to 10% in adulthood. Whether these lower carriage rates among adults are the result of acquisition of immunity, lower contact or transmission rates among these age groups, or the two effects combined, is still a matter of debate. These interactions are complicated further by the large diversity of the organism (over 90 different serotypes have been isolated) and the different immunogenic and pathogenic properties of these serotypes (Kalin, 1998).

A 23-valent pneumococcal polysaccharide vaccine has been available for decades and has been recommended for use in the UK since 1992 for people with medical conditions for whom pneumococcal infection is likely to be more common or serious (at-risk groups) (Salisbury & Begg, 1996). Although the 23 serotypes contained in the vaccine account for over 90% of the pneumococcal isolates causing serious infection in England and Wales (George & Melegaro, 2001), uncertainty about the level of protection conferred by the vaccine among individuals at the extremes of age as well as among at-risk groups has limited its widespread use. Moreover the vaccine is generally unsuitable for use within a routine mass vaccination programme because of its poor immunogenicity in young children and short period of protection (3-5 years) (Konradsen, 1995;Sankilampi *et al.*, 1997). Similar problems had earlier limited the use of a polysaccharide vaccine against *Haemophilus influenza* type b

(Hib) disease and later on *Neisseria meningitidis* serogroup C (MenC) disease, but these difficulties were overcome by conjugating respectively the Hib and MenC capsular polysaccharide to an immunogenic protein such as diphtheria or tetanus toxoid. Using a similar manufacturing technology, a pneumococcal conjugate vaccine, which contains polysaccharide from seven common capsular types, became available in 2002 and was recommended for immunisation of at-risk groups under the age of two years and very recently (2004) extended to at-risk children below five years. Moreover, the UK recommendation that was introduced in 2000 that all elderly (65+) should receive the influenza vaccine provided an opportunity for the 23-valent pneumococcal vaccine for all elderly, since both vaccines may be given at the same time. The recommendation for the polysaccharide vaccine was thus modified in 2003, including healthy elderly 65+ years of age in the at-risk categories.

While discussions are ongoing on whether or not to include the pneumococcal conjugate vaccination programme in the infant immunisation schedule, a number of questions on the long-term effects of the vaccine remain still unanswered (Pelton *et al.*, 2003;O'Brien & Dagan, 2003;Peltola *et al.*, 2004). Moreover, in contrast to the plain polysaccharide vaccine, the conjugate vaccine also seems to have an impact on *S.pneumoniae* colonisation rates, inducing not only a reduction in the prevalence of carriage of vaccine serotypes among vaccinated individuals (and also among their siblings), but also an increase in the prevalence of non-vaccine serotypes. These can now occupy the ecological *niche* that was previously almost fully occupied by the vaccine types. Whether this effect will have repercussions on the overall incidence rates of pneumococcal disease is not straightforward as it depends on the properties of the serotypes that are taking over; their relative invasiveness as well as the host response to their presence. Some evidence is already available on an increase of pneumococcal disease caused by serotypes not contained in the vaccine, both non-invasive clinical manifestations, such as otitis media (Eskola *et al.*, 2001), as well as more serious invasive disease (Kaplan *et al.*, 2004). These indirect effects have to be taken into account when considering the impact of vaccination programmes and when performing economic evaluations of public health interventions.

The role of mathematical modelling has become progressively more important in guiding vaccine policy decisions (Salisbury *et al.*, 2002) and, together with economic analysis (Edmunds *et al.*, 1999), provides additional information to policy decision makers regarding the potential impact and its economic acceptability. Through models we can gain a better understanding of the transmission dynamics of infectious organisms, we can investigate the observed pattern of disease and its epidemiology and we can predict the potential impact of alternative public health interventions, such as vaccination. However, models are necessarily simplifications of the real world, and thus their applicability is restricted by the availability of sound parameter estimates and realistic model assumptions. For extremely diverse organisms, such as *S.pneumoniae*, for which a comprehensive understanding of the biology is far from achieved, realistic model parameterisations are not always easy to formulate and still represent a challenge.

The broad research aims of this PhD project were:

1. To describe the epidemiology of pneumococcal invasive and non-invasive disease in England and Wales;
2. To further the understanding of pneumococcal carriage, to estimate pneumococcal transmission parameters and to investigate serotype specific differences;
3. To use models to predict the impact of the UK vaccination programme and to investigate a range of alternative vaccination schedules;
4. To evaluate the cost-effectiveness of the vaccination programme with the 23-valent polysaccharide vaccine;
5. To evaluate the cost-effectiveness of universal infant vaccination with the 7-valent conjugate vaccine taking into account herd immunity effects and potential serotype replacement.

The thesis structure is as follows. Chapter 2 provides an overview of *S.pneumoniae* and highlights the essential features of carriage, disease, epidemiology and control. In particular, an overview of the pathogenesis of *S.pneumoniae* is presented at the beginning of the chapter,

from its microbiological composition to the way in which this interacts with human host. This is followed by a description of the clinical manifestations and the development of pneumococcal vaccines. The available national surveillance systems on pneumococcal disease conclude the chapter. In Chapter 3 the epidemiology of pneumococcal disease is investigated and estimates of the current burden of disease in England and Wales are provided. Both invasive and non-invasive conditions are considered and comparisons between laboratory reports, hospitalisations and consultations to the general practitioner (GP) are made. Chapter 4 is the first of two chapters examining the effectiveness and cost-effectiveness of the 23-valent polysaccharide pneumococcal vaccines among the elderly. Here a systematic literature review of published randomised controlled trials on the pneumococcal polysaccharide vaccine efficacy is performed. Meta-analysis techniques are applied in order to estimate the overall pooled efficacy level among elderly at high and low-risk of pneumococcal infection. These results inform the cost-effectiveness analysis of the next chapter. Chapter 5 determines the costs associated with treatment of pneumococcal disease in the elderly and performs an economic evaluation of what was, at the time of the analysis, the pneumococcal vaccination programme with the plain polysaccharide vaccine among high-risk elderly. Possible extensions of the programme, which were under discussion at the Department of Health when this PhD project started, are also considered (indeed the results of this work helped inform the national policy debate). Chapter 6 moves the focus away from pneumococcal disease, towards pneumococcal carriage. Here, longitudinal data for pneumococcal carriage in UK households are for the first time analysed with a statistical model that takes into account the family effect on the transmission dynamics of pneumococci. This chapter and the following one, which extends the model to include serotype-specific information, lay the foundations for further modelling work and parameterisation of Chapter 8. Chapter 7 takes forward the modelling framework developed in Chapter 6 to include serotype specific data as well as individual risk factors for pneumococcal carriage that were available for the study population. Here, serotype-specific differences in pneumococcal transmission dynamics are investigated, and estimates of the duration of carriage for the most prevalent types are produced. In Chapter 8 a realistic age-structured transmission dynamic model is developed using parameter estimates obtained in the previous chapters. The model is used to investigate the impact of vaccination

on pneumococcal carriage and, in particular, the dynamics of vaccine *vs.* non-vaccine serotypes. In Chapter 9 a static cohort model is used to generate estimates of the cost per life year saved by a routine infant vaccination with the pneumococcal conjugate vaccine from the perspective of the health care provider (the NHS). The effects of the indirect effects of vaccination (herd immunity and serotype replacement) are considered in the model. Finally, in Chapter 10, the implications of this work and future directions for research are discussed.

CHAPTER 2 - BACKGROUND

2.1 Introduction

Streptococcus pneumoniae is one of the most important bacterial pathogens in respiratory tract infections, affecting children and adults worldwide (Booy & Kroll, 1994;Booy *et al.*, 1995;Fedson *et al.*, 1999a;Robinson *et al.*, 2001;Cartwright, 2002). It is a common component of the nasopharyngeal flora in healthy individuals although it is also responsible for causing a variety of infections ranging from upper respiratory tract infections, ear infections and sinusitis, to more serious diseases such as pneumonia, septicaemia and meningitis (Miller *et al.*, 2000;Kaltoft *et al.*, 2000;Spanjaard *et al.*, 2000;Eriksson *et al.*, 2000;Syriopoulou *et al.*, 2000;Kyaw *et al.*, 2002).

Asymptomatic carriage of *S.pneumoniae* is common, especially among children, and the existence of almost 90 different pneumococcal serotypes whose prevalence varies in different geographical regions adds complexity to the already diverse epidemiology of pneumococcal disease around the world (Bruyn *et al.*, 1992).

A number of different data sources are available for England and Wales to monitor disease incidence rates over time and to assess whether any change will occur as a result of new vaccination programmes in both the incidence of invasive and non-invasive disease. Ongoing surveillance is necessary to better ascertain the effectiveness of the programme and to detect any potential harmful indirect effect, such as serotype replacement, that vaccination may produce and that may also increase disease severity.

The aim of this chapter is to provide an overview of the pneumococcus and to highlight the essential features of carriage, disease, epidemiology and control. The literature review related to the modelling and economics of pneumococcal infection and vaccination is not included in the current chapter but will be provided in the relevant parts of the thesis. The current chapter is divided into four components. First, an overview of the pathogenesis of *S.pneumoniae* will be presented, from its microbiological composition to the way in which this interacts with the human host. This is followed by a description of the clinical manifestations of pneumococcal infection and the risk factors associated with disease. Thirdly, the development of vaccines and the roles of vaccines in the control of pneumococcal carriage and disease are reviewed. The chapter ends with a description of the national surveillance systems.

2.2 The organism

Isolated first in 1880 from carriers of the organism in the United States (Stenberg, 1881) and in France (Pasteur, 1881) (Watson & Musher, 1999), *Streptococcus pneumoniae*, or the pneumococcus, is one of the most important bacterial pathogens in respiratory tract infections, still affecting children and adults worldwide despite the use of antibiotics and the development of vaccines (Fedson *et al.*, 1999a;Robinson *et al.*, 2001). The main reservoir is the nasopharynx and the possible outcomes, once colonisation has taken place, may be clearance of the organism, the asymptomatic persistence for several weeks (the carrier state), or the progression to disease (Cundell *et al.*, 1995;Schaechter *et al.*, 1998). When this occurs, the bacteria can either spread to adjacent mucosal tissues, causing mucosal infection (otitis, sinusitis and pneumonia) (Block, 1997;Brown & Lerner, 1998;Marrie *et al.*, 2002), or else invade the bloodstream, or other sterile sites, producing an invasive disease condition (sepsis or bacteraemia, meningitis) (Miller *et al.*, 2000;Shackley *et al.*, 2000).

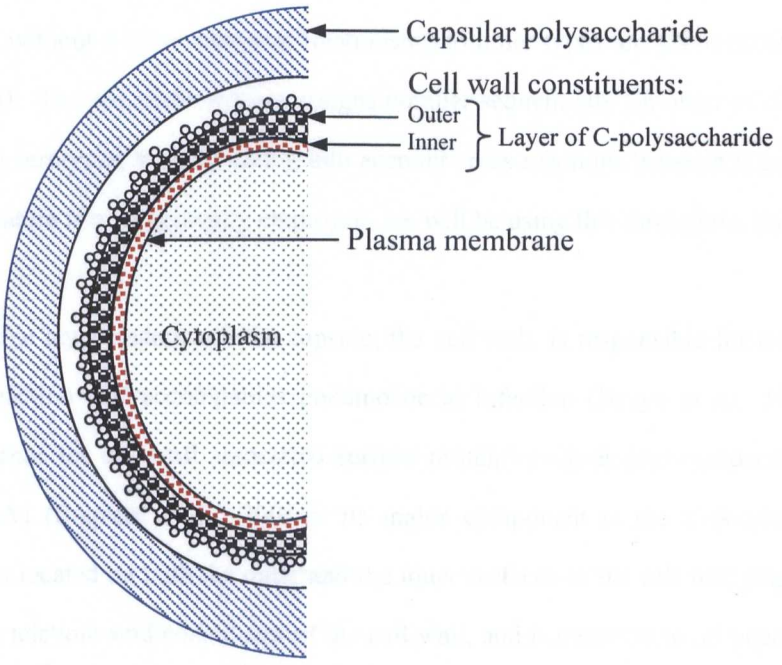
2.2.1 Cell surface structure

The pneumococcal cell surface structure is the part of the organism that primarily interacts with host factors, immune cells, and epithelial surfaces. The majority of pneumococci are

encapsulated, and although many of the interactions between host factors and the bacteria involve the capsular polysaccharide that coats the outermost surface of pneumococci, other components of the cell surface, located under the capsule, have a role in the interaction between host and bacteria.

The pneumococcal outer surface consists of three parts: the capsule, the cell wall and the plasma membrane (Figure 2.1).

Figure 2.1- Schematic illustration of pneumococcal outer surface



The capsular polysaccharide (CPS). The capsule of the pneumococcus represents the most important virulence factor of the organism because it protects the bacterium from phagocytosis (Magee & Yother, 2001;Bogaert *et al.*, 2004a). Non-capsulated variants are incapable of causing progressive disease unless injected in overwhelmingly large numbers (Austrian, 1984). To date, almost 90 different capsular serotypes have been described (Bruyn *et al.*, 1992), six of them quite recently (Henrichsen, 1995). The serotypes differ in the chemical structure of their CPS and in the capability of the immune system to recognise these structural differences and to respond with specific antibodies (Tomasz, 2000). The virulence

of each capsular type is associated with both the quantity of capsular polysaccharide produced and, most importantly, the chemical structure of the capsule, which is known for most of the serotypes (Kamerling, 2000). The frequency of the capsular types varies by time, geographic areas and age group and it may be linked to both evolutionary patterns of the organism and to the level of serotype-specific immunity of individuals.

Two different systems of nomenclature exist to define the capsular types: the Danish system and the American system. The Danish system is based on cross-reaction between types, so that antigenically related serotypes are assigned to a common serogroups, with individual serotypes within each group distinguished by the trailing letter (e.g. 6A and 6B, 9A, 9L, 9N and 9V). Types without a close antigenic relationship to other types are given numbers only (i.e. 1, 2, 3, 4, 5). The American system assigns number sequentially (in order of discovery) to the individual serotypes, without taking into account cross-reactions between types. As the Danish nomenclature is now generally employed, we will be using this throughout this thesis.

The cell wall. The layer underneath the capsule, the cell wall, is responsible for the intense inflammatory reaction that accompanies pneumococcal infection (Bruyn *et al.*, 1992) and serves as an anchor for cell-wall associated surface proteins such as pneumococcal surface adhesin A (PsaA) (Bogaert *et al.*, 2004a). Its major component is the C-polysaccharide antigen, which is located on both the outer and the inner surfaces of the cell wall (Figure 2.1) and includes the teichoic acid constituent of the cell wall, and is common to all pneumococci (Tomasz, 1981). Antibodies to the C-polysaccharide, common to most of the 90 different serotypes, start developing in children after the age of 5 months and increase steadily thereafter as a consequence of exposure to pneumococcus through carriage or infection. Nearly all children develop some antibody by the age of 4 years (Gray *et al.*, 1983).

The plasma membrane. The plasma membrane is situated on the inner inside of the cell wall and is composed of lipoteichoic acid, lipid and protein (Bruyn *et al.*, 1992). It also contains the Forssman antigen (F-antigen), which is common to all pneumococci and functions as a powerful and highly specific inhibitor of pneumococcal autolysin (Tomasz, 1981).

2.2.2 Colonisation and pathogenesis

Colonisation. The bacterium gains entry into the host by colonising the nasopharyngeal mucosal epithelium. Attachment is thought to be mediated through a specific bacterium-derived adhesin molecule that forms a bridge between bacterial surface components and epithelial cell receptors (Ghaffar *et al.*, 1999). The outcome of colonization is determined by the intrinsic virulence of the colonizing serotype and the efficiency of the host defence mechanism. Some serotypes are more virulent and more likely to cause severe disease; others are less virulent and are usually only isolated from the nasopharynx of asymptomatic persons. Only a small proportion of colonisations progresses to disease (~15%)(Gray *et al.*, 1980). The interval between colonization and onset of disease, though variable, is usually short (Gray *et al.*, 1980;Schaechter *et al.*, 1998;Ghaffar *et al.*, 1999). One individual may become colonized many times, usually with different serotypes. Moreover, simultaneous carriage of two, or more, *S.pneumoniae* serotypes has been demonstrated (Gratten *et al.*, 1989;Huebner *et al.*, 2000). More on this will be presented in section 2.2.4.

Progression to disease. After colonising the nasopharynx, *S.pneumoniae* may spread locally, either upward into the Eustachian tube and the middle-ear cavity to produce otitis media, or downward into the alveoli of the lower respiratory tract to cause lobar pneumonia (Cundell *et al.*, 1995). At this point, if the host defence mechanism is not able to confine the pneumococcus to the lungs or middle ear, it may spread causing a bacteraemic infection or invade the cerebrospinal fluid (CSF) leading to meningeal inflammation (Austrian, 1984).

Transmission. Transmission from a sick person or, more commonly, from an asymptomatic carrier, is via droplets of respiratory secretions that may remain air-borne over a distance of up to one meter. The infecting organism may also be carried on hands contaminated with secretions. Transmission occurs mainly within the family and closed institutions such as day-care centres (Givon-Lavi *et al.*, 2002). Because there are many more asymptomatic carriers than diseased people, most of the links in the chains of transmission are unobserved.

2.2.3 Virulence

Although the pneumococcal polysaccharide capsule is still considered the primary virulence factor for *S.pneumoniae* (Kalin, 1998), recent studies have suggested that certain proteins displayed on the surface of gram-positive organisms significantly contribute to its pathogenesis. These, as summarised in Table 2.1, are involved in the disease process caused by these pathogens interacting with the host cells and in facilitating the invasion and spread of the organism in the host environment (Jedrzejas, 2001).

Table 2.1 - Outer membrane proteins

Protein	**Function**
Pneumococcal surface protein A (PspA)	Interferes with host complement system reducing the complement mediated clearance and phagocytosis of pneumococci
Hyaluronate lyase (Hyl)	It enhances the host membrane cleavage facilitating bacterial invasion
Pneumolysin (Ply)	Cytoplasmatic enzymes. Released upon autolysis. Facilitates the spread of Pnc infection, suppressing the host inflammatory and immune response
Autolysin (LytA)	Involved in cell wall degradation which facilitates the release of the components of the cell wall shown to be highly inflammatory
Pneumococcal surface antigen A (PsaA)	It stabilises cell wall structure and it also modulates the transport of metals inside cytoplasm of pneumococci, possibly causing toxic effects on host cells.
Choline binding protein A (CbpA)	Interacts with immune mediated host cells preventing them to be effective. This process might be involved in advancing pneumococcal disease from colonisation to invasion.
Neuraminidase	Enhances colonisation and adherence damaging host cells membrane

The information on the table were abstracted from Jedrzejas MJ (2001)

2.2.4 Laboratory diagnosis

The isolation of *S.pneumoniae* from blood, CSF or other normally sterile body sites is the requirement that is needed in order to confirm the aetiological diagnosis of a clinical manifestation that may be related to a pneumococcal infection. Bacterial culture still remains the most frequently used method to detect pneumococcus from a variety of clinical specimens

(Lankinen, 2003). It is routinely used in clinical diagnosis of suspected invasive infections although the low levels of sensitivity that have been found, partly as a result of prior administration of antibiotics, seriously limit its utility. The value of culture methods in diagnosing pneumococcal pneumonia is still very much debated, with 48% to 94% of confirmed bacteraemic pneumococcal pneumonia patients having the organism isolated from sputum samples (Drew, 1977) and extremely low sensitivity levels (27%) for culture of nasopharyngeal swabs in adult patients with community-acquired pneumonia (CAP) (Hedlund *et al.*, 1990).

Traditional non-cultural techniques include microscopic examination of Gram stained specimens (i.e. urine, blood or CSF) and antigen detection with a range of immunoassays (e.g. by latex agglutination). The former provides a visual assessment of the presence of pneumococci in the specimen, evaluating the reaction to the Gram staining (i.e pneumococcus is a Gram-positive bacterium and stains purple) which correlates to differences in the cell wall structure of the organism. Antigen detection methods, on the other hand, are procedures that measure the presence of specific microbial antigens. Although these tests give results within minutes of receipt of the specimen, their sensitivity is not significantly greater than the Gram stain and false positive results may occur due to cross reactive antigen (Mims *et al.*, 1995). A rapid immunochromatographic membrane assay (Binax NOW *S.pneumoniae* Urinary Antigen Test, Binax, Portland ME, USA) has been approved for the diagnosis of pneumococcal pneumonia in adults (Henney, 1999). Differently from other antigen tests, that detect capsular antigens, this test detects C-polysaccharide cell wall antigen common to all *S.pneumoniae* serotypes. Various studies have demonstrated high levels of both sensitivity and specificity among adults with bacteraemic pneumococcal pneumonia (~80% sensitivity and ~90% specificity) (Murdoch *et al.*, 2001;Dominguez *et al.*, 2001;Smith *et al.*, 2003) although sensitivity in children remains low (11-50%) (Dowell *et al.*, 2001;Hamer *et al.*, 2002). The NOW test appeared to be very sensitive and specific in detecting pneumococcal antigen in the CSF of patients with pneumococcal meningitis (Marcos *et al.*, 2001;Samra *et al.*, 2003).

Serological diagnosis by enzyme linked immunoabsorbent assay (ELISA) is used to diagnose infections measuring any antibody response, regardless of immunoglobulin class, or to detect class specific antibody. The major disadvantages of diagnoses based on serology are that it requires both acute and convalescent sera and it is retrospective, as 2-4 weeks must elapse before IgG antibodies, produced in response to infection, are detectable in the serum (Mims *et al.*, 1995). However, serological diagnosis is of great value when the organism is difficult to culture or when the individual has to be screened for several different infections simultaneously. Moreover, it provides information not only for the diagnosis of a clinical manifestation but also for the evaluation of exposure, and consequent asymptomatic carriage of a specific pathogen.

Advances in molecular biology have resulted in new techniques for the genotypic identification and characterisation of microorganisms. Nucleic acid amplification using the polymerase chain reaction (PCR) is considered a very sensitive and specific non-culture diagnostic technique for the detection of pathogens in a clinical specimen. In these techniques genomic sequences specific for infectious agents, such as the pneumococcus, are selected, cloned, synthesised and used as probes. These probes can bind with high specificity to complementary sequences of target nucleid acid of the pathogen. PCR techniques can be applied to different clinical specimens such as blood, CSF, urine and sputum although due to the high levels of sensitivity of this test (Dagan *et al.*, 1998), cross contamination resulting in false positives may occur and, thus, appropriate treatment of biological materials is one of the most important steps carried out in molecular microbiology.

Detecting carriage. Pneumococcal carriage is detected by isolating the organism from the human nasopharynx. The isolation rate may change according to variations in sampling methods, delays prior to culturing and differences in culture techniques (Rapola *et al.*, 1997). Several studies (Gray *et al.*, 1980;Capeding *et al.*, 1995;Rapola *et al.*, 1997) have shown that nasopharyngeal sampling is better than oropharyngeal sampling for detecting *S.pneumoniae*, and that although nasopharyngeal aspirates (NPA) are superior for the detection of

pneumococci, nasopharyngeal swab specimens are adequate when the NPA is not available (i.e. healthy children or children with no obtainable secretions) (Rapola *et al.*, 1997).

Serotyping. Serotyping of pneumococcal isolates is usually performed with the Quellung reaction method, in which cultured isolates are blended with group or type-specific antisera, and the capsular swelling reaction is observed under a microscope (Henrichsen, 1999). Other typing methods include: capillary precipitin typing (Russell *et al.*, 1978), counterimmunoelectrophoresis (Leinonen, 1980), latex agglutination (Arai *et al.*, 2001) and coagglutination (Lalitha *et al.*, 1996).

Most carriage studies select only one colony from a plate for further serotyping and so are unable to detect simultaneous carriage of multiple strains. Studies that perform "multiple picks" are laborious and expensive. However, Huebner and colleagues (2000) detected simultaneous carriage of 2 serogroups in only 1.3% and 2.4% of the specimens examined in, respectively, South Africa and Israel. A similar percentage (1.2%) was found when up to 5 colonies were examined. A much higher rate of simultaneous colonisation was found by Gratten and colleagues (1989) who found that 29.5% of 156 children in Papua New Guinea were colonised by multiple pneumococcal serotypes. In the FinOM cohort study, the proportion of carriers with two or more serotypes found in the (healthy) nasopharyngeal samples of 649 children was 3.7% (Syrjanen *et al.*, 2001).

2.3 Pneumococcal disease

2.3.1 Clinical conditions

A very diverse spectrum of clinical manifestations may result from infection with the pneumococcus, from relatively benign infections, which may or may not have long-term consequences (i.e. conjunctivitis, ear infections, sinusitis), to more serious invasive disease, which may result in the death of the patient (i.e. septicaemia, meningitis). A comprehensive review of the unusual manifestations of invasive pneumococcal infection can be found in

Taylor and Sanders (1999). Moreover, antimicrobial resistance in pneumococci has also been associated with rare or particularly severe disease forms (Saenz *et al.*, 1998;Go *et al.*, 1998) and, also, with nosocomial infections (Cimolai *et al.*, 1999;de Galan *et al.*, 1999;Weiss *et al.*, 2001).

Acute otitis media (AOM). Acute otitis media, or middle ear infection, is predominantly a disease of infancy and early childhood, which can progress from a number of different bacterial and viral infections, the most important of which are: *S.pneumoniae*, *H.influenza*, *Moraxella catarhalis*, respiratory syncytial virus, influenza virus and rhinovirus (Faden *et al.*, 1997;Rovers *et al.*, 2004). *Streptococcus pneumoniae* has been implicated, in particular, with recurrent AOM (Black *et al.*, 2000). Although it is not a life-threatening condition in itself, it can cause serious chronic complications (i.e. recurrent AOM episodes before the age of 3 years can have adverse long-term consequences in school performance (Luotonen *et al.*, 1998)) and is a major public health problem worldwide (Klein, 2000). Symptoms of AOM may include some or all the following: irritability, crying, ear pain, fever, feeding problems, vomiting and hearing impairment. These symptoms are frequently associated with signs of respiratory infection, such as runny nose or cough. Severe ear infections can also cause the rupture of the eardrum, which will then lead to pus draining out of the middle ear into the ear canal. The eardrum rupture usually heals after medical treatment. Infants and young children are very susceptible to pneumococcal acute otitis. The flow of bacteria and viruses from the throat to the middle ear is also facilitated by the shape of the tube connecting the throat to the middle ear (Eustachian tube) which, in children, appears to be shorter, wider and more horizontal (Rovers *et al.*, 2004). Diagnosis of AOM is usually clinical and treatment with antibiotics for a week to 10 days is usually effective, although improvement has been seen in around 80% of the children with AOM within 2-14 days without any medical interventions (Rovers *et al.*, 2004).

Community-acquired pneumonia (CAP). Pneumonia is an inflammation of the lungs caused by infection with bacteria, viruses and other organisms. It is usually triggered when the host defence system is weakened, which most often occurs as a consequence of viral

upper respiratory infection. S*treptococcus pneumoniae* is one of the most frequent causes of bacterial pneumonia with 20-60% of all episodes of CAP requiring hospitalisation and 9-20% of outpatients visits being related to pneumococcal infection (Bartlett & Mundy, 1995). Further insights on this will be presented in Chapter 3. Symptoms generally include a sudden onset with a single shaking chill that is usually followed by fever with cough, sputum production, and chest pain. Extra-pulmonary symptoms such as nausea, vomiting or diarrhoea and headache are reported in 10-30% of patients with CAP (Brown & Lerner, 1998;Marrie, 2000). Serious and potentially lethal complications of pneumococcal pneumonia include progressive pneumonia, sometimes associated with the adult respiratory distress syndrome and/or septic shock, empyema (infection of the pleural space), pericarditis (inflammation of the sac around the heart) and endobronchial obstruction. Some patients develop pulmonary super-infections, which consists of a temporary improvement during treatment followed by deterioration, with recurrence of fever and worsening pulmonary infiltrates.

The most important diagnostic test for CAP is the chest radiograph. X-ray examinations help distinguish pneumonia from other conditions and can provide information on the severity of illness and the presence of other coexisting conditions such as bronchial obstruction or pleural effusion.

Bacteraemia. When the host immune mechanism fails to confine the pneumococcus to the lung, the organism may spread via the pulmonary lymphatics to the hilar lymph nodes and via the thoracic duct to the systemic circulation, causing a bacteraemic infection (Austrian, 1984). It may also arise as a consequence of pneumococcal meningitis (Austrian, 1964) and from organisms colonising the respiratory mucosa of the nasopharynx, entering the lymphatic vessels and, finally, gaining access to the blood. Non-specific symptoms occur such as fever and irritability.

Meningitis. Pneumococcal meningitis is an inflammation or infection of the membranes covering the brain and spinal cord which may arise in a variety of ways (Austrian, 1984), progressing from pneumonia and bacteraemia or else as an extension of a middle ear infection

or paranasal sinuses that involve the bony structure of the skull and ultimately the meninges. Direct migration of organisms colonising the upper respiratory tract to the subarchnoid space may also occur following the fracture of the skull. High fever, headache and stiff neck are the common symptoms of meningitis in anyone over the age of 2 years. Other symptoms may include nausea, vomiting, discomfort looking into bright lights, confusion and sleepiness. In newborns symptoms may be less specific (i.e. fever, irritability, inability to feed and drowsiness), and may be more difficult to detect. Unlike meningococcal disease, pneumococcal meningitis is not usually associated with any skin rash. Once meningitis is diagnosed, antibiotic treatment should be started, even before hospitalisation (Booy & Kroll, 1994).

2.3.2 Outcome (mortality rate and sequelae)

Despite the advent of antibiotic therapies, mortality associated with invasive pneumococcal infection has remained high, ranging from 6% to 19% in uncomplicated hospitalised cases of pneumococcal pneumonia (Mufson, 1981) and three to four times higher levels for pneumococcal pneumonia patients with a bacteraemic infection (Laurichesse *et al.*, 1998) (See also Chapter 3). The clinical outcome of bacterial meningitis varies according to socioeconomic aspects (developed or developing countries), age and causative pathogen (Baraff *et al.*, 1993;Koedel *et al.*, 2002). Mortality rates for meningitis due to *S.pneumoniae* infection is higher than for any other bacterial aetiology, with reported case-fatality ratio (CFR) in the range of 15.3% (Baraff *et al.*, 1993) to 30% (Mufson, 1981), with higher case-fatality rates in the very young and in the elderly (Laurichesse *et al.*, 1998;Berezin *et al.*, 2002) and in those infected with antibiotic resistant pneumococci (Berezin *et al.*, 2002). Of the survivors, up to 30% develop long-term sequelae (Koedel *et al.*, 2002), including mental retardation, sensorineural hearing loss, motor deficit and seizure disorder (Baraff *et al.*, 1993;Pikis *et al.*, 1996;Arditi *et al.*, 1998;Bedford *et al.*, 2001). Language difficulties and school learning impairment have been reported also following chronic and recurrent middle-ear disease, especially when occurring under the age of 3 years (Luotonen *et al.*, 1998).

2.3.3 Antimicrobial resistance

The increasing incidence of antimicrobial resistant *S.pneumoniae* isolates is becoming a problem worldwide (Campbell & Silberman, 1998;Saha *et al.*, 1999;Rudolph *et al.*, 2000;Hyde *et al.*, 2001;Aspa *et al.*, 2004) with penicillin non-sensitive rates as high as 50% in France and Spain (Fenoll *et al.*, 1998;Felmingham & Gruneberg, 2000) and 16%-25% in the USA (Hofmann *et al.*, 1995;Campbell & Silberman, 1998) and up to 20% in other European countries (Reacher *et al.*, 2000;Jacobs *et al.*, 2003). Previous use of β-lactam antibiotics, alcoholism, and non-invasive disease have been associated with penicillin resistant strains (Clavo-Sanchez *et al.*, 1997;Nasrin *et al.*, 2002), whereas the extremes of age (<5 and 65+ years) and the previous use of β-lactam antibiotics in non-invasive disease cases were found to be risk factors for multidrug resistant pneumococci (Clavo-Sanchez *et al.*, 1997). In addition, chronic pulmonary disease, HIV infection, and previous hospital admission have all been associated with penicillin-resistant pneumococcal pneumonia (Aspa *et al.*, 2004).

There is evidence of serotype-specific differences in antibiotic susceptibility patterns, with serotypes 14, 6B and 23F accounting for most of the resistant strains (Munoz *et al.*, 1991;Fenoll *et al.*, 1998;Saha *et al.*, 1999;Rudolph *et al.*, 2000;Hyde *et al.*, 2001).

2.3.4 Risk factors associated with disease

The risk of developing pneumococcal disease is influenced by a number of factors, which are related to the characteristics of the invading organism, the host defence mechanisms (carrier) as well as to the environmental conditions to which the carrier is exposed. It is usually the combination of all these factors that determine the severity and invasiveness of the clinical manifestation.

Agent factors. The encounter of the organism is clearly the first step that is needed in order for the individual to then progress to disease. Colonisation and asymptomatic carriage in healthy individuals depend on a number of factors associated with the bacteria and its

relationship with the host immune system. A number of carriage studies have shown that carriage is inversely related to the age of individuals, with carriage rates as high as 60%-70% in children less than 2 years of age (Gray *et al.*, 1980;Coles *et al.*, 2001) and a steady and consistent decline thereafter (Leino *et al.*, 2001) (Table 2.2). This can be the result of both the poorer immunity defences of young children and the close contacts they experience during childhood (Ghaffar *et al.*, 1999).

In addition, several studies have shown significant serotype specific differences in relation to acquisition rates, duration of carriage and invasiveness (Smith *et al.*, 1993;Kalin, 1998;Hausdorff *et al.*, 2000a;Hausdorff *et al.*, 2000b;Brueggemann *et al.*, 2003), with some serotypes (i.e. 1, 4, 14, 7) being found more often among invasive pneumococcal disease patients than among asymptomatic carriers (Brueggemann *et al.*, 2003). More on the relationship between pneumococcal carriage and disease will be covered in Chapter 6.

Host factors. Several host factors are associated with an increased risk of pneumococcal disease given carriage: the extremes of age, non-immunological defects and immunological ones, both inherited and acquired (Gillespie, 1989).

Individuals at the extremes of age (<2 years and 65+) are generally considered at high-risk of pneumococcal infection, experiencing the highest rates of both invasive and non-invasive pneumococcal conditions (George & Melegaro, 2001). Although in infants this is thought to be associated with an immature immune system and a lack of acquired immunity, the high incidence among the elderly is not completely understood and may be related to increasing rates of immunocompromising conditions, such as congestive heart failure, diabetes mellitus and haematological malignancies (Obaro *et al.*, 1996b).

A number of non-immunological and immunological defects increase individual susceptibility to pneumococcal infection (Obaro *et al.*, 1996b). Whereas the former (e.g. skull fracture, damage to bronchial epithelium as occurs with influenza viral infection) disrupt the natural barriers of the host facilitating the entrance of the organism and leading to recurrent and

severe pneumococcal infection (Johnston, Jr., 1991), the latter increase the risk of invasion through an inadequate production of antibodies (Siber *et al.*, 1980;Douglas *et al.*, 1983). Persons with human immunodeficiency virus (HIV) infection have an increased incidence rate of pneumococcal disease (Nuorti *et al.*, 2000b). McEllistrem and colleagues (2002) found that recurrent pneumococcal infection is 6 times more common in HIV-positive persons than in persons without HIV infection. Asplenia is associated with increased susceptibility to pneumococcal infection being the organism responsible for 50% of the cases of bacterial septicaemia in asplenic patients (Wara, 1981).

Table 2.2 - Pneumococcal nasopharyngeal colonisation rate and antibiotic resistance

Setting	Year	Number of individuals	Risk group	Age	Carriage Rate (%)	Antibiotics	Resistance (%)	Reference
UK	2000-2001	489	Healthy	0-72 yrs	8-52**	Penicillin/Erythromycin	3.7/10	Hussain *et al.*(2004a)
India	1998-1999	464	Healthy	2-6 mths	54-70*	-	-	Coles *et al.*(2001)
Israel	1993-1994	514	Healthy	2-24 mths	26-62*	1+ antibiotics	11-27*	Dagan *et al.*(1996b)
Gambia	1989-1991	113	Healthy	< 5 yrs	76	-	-	Lloyd-Evans *et al.*(1996)
USA	2001	401	Healthy	0-6 yrs	48.2	Penicillin/Erythromycin	36.7/23.3	Reges-Yochay *et al.*(2004)
USA	2001	899	Healthy	18+ yrs	3.4	Penicillin/Erythromycin	26.5/6.1	Reges-Yochay *et al.*(2004)
Finland	1994-1997	329	Healthy	2-24 mths	13-43*	-	-	Syrjanen *et al.*(2001)
Greece	1997-1999	2448	Healthy	2-23 mths	31	Erythromycin	18	Syrogiannopoulos *et al.*(2002)
USA	1994-1995	245	Healthy	<2/2-5/>5 yrs	77-35-13	Penicillin	41	Steele *et al.*(1996)
Finland	1994-1997	210	Healthy	0-11 yrs	2.5-27**	-	-	Leino *et al.*(2001)
Italy	1996	1273	Healthy	1-7 yrs	3-3.8**	Penicillin/Erythromycin	5/40	Principi *et al.*(1999)
USA	2001	404	Healthy/URTI	0-6 yrs	42[c]-68[d]-46[e]	Penicillin/Erythromycin	36.7/23.3	Regev-Yochay *et al.*(2004)
Gambia	1989-1991	81	IPD	< 5 yrs	90	-	-	Lloyd-Evans *et al.*(1996)
France	1996	71	Orphanage	0-24 mths	57.4	Penicillin	94	Raymond *et al.*(2000)
Portugal	1997-2000	466	PED	0-12 yrs	25-39	Penicillin	23	Neto *et al.*(2003)
USA	1994-1995	312	SCD	2 wks-18 yrs	13	Penicillin	55	Daw *et al.*(1997)
USA	1994-1995	351	SCD	<2/2-5/>5 yrs	33-10-6	Penicillin	62	Steele *et al.* (1996)
USA	2001	173	URTI	0-6 yrs	56.9	Penicillin/Erythromycin	36.7/23.3	Regev-Yochay *et al.*(2004)
USA	2001	192	URTI	18+ yrs	6.3	Penicillin/Erythromycin	26.5/6.1	Regev-Yochay *et al.*(2004)
Finland	1994-1997	329	URTI	2-24 mths	45-56*	-	-	Syrjanen *et al.*(2001)
Finland	1994-1997	329	AOM	2-24 mths	22-45*	-	-	Syrjanen *et al.*(2001)
Israel	1996-1997	264	DCC	12-35 mths	77	Penicillin	27[a]-48[b]	Givon-Lavi *et al.*(1999)
Italy	1999	610	DCC	2-65 mths	15	Penicillin/Erythromycin	19/52	Petrosillo Syrjanen *et al* (2002)

* increases with age; ** increases with decreasing age ; AOM=acute otitis media; IPD=invasive pneumococcal disease; SCD=sickle cell disease; URTI=upper respiratory tract infection; PED = pediatric emergency department; DCC = day-care centres; [a]24-35 mths; [b]12-23 mths; [c]<12 mths;[d]24-35 mths; [e]48-72 mths;

Socio-economic and environmental factors. Independent determinants of nasopharyngeal colonisation are environmental features and socio-economic factors such as crowding, family size (i.e. number of siblings), income, smoking (active and passive) and recent antibiotic use.

Crowding, as occurs in hospital, day-care centres and prisons, increases horizontal spread of pneumococcal strains and is, thus, a major risk factor in nasopharyngeal colonisation (Bogaert *et al.*, 2004a). Several studies have demonstrated a strong association between day-care attendance and higher risk of colonisation by *S.pneumoniae* (Givon-Lavi *et al.*, 1999;Principi *et al.*, 1999;Raymond *et al.*, 2000;Neto *et al.*, 2003;Regev-Yochay *et al.*, 2004), and, in particular, with antibiotic resistant strains (Henderson *et al.*, 1988;Steele *et al.*, 1996;Dagan *et al.*, 1996b). Evidence of genetic clustering among pneumococcal isolates in both day care centres (Bogaert *et al.*, 2001) and prisons (Hoge *et al.*, 1994), have been shown and support the idea of horizontal transmission of specific pneumococcal strains.

Family size, and specifically the number of older siblings, has been associated with nasopharyngeal carriage of *S.pneumoniae* in children (Dagan *et al.*, 1996b;Petrosillo *et al.*, 2002). Moreover, the exposure to other family members colonised with a particular pneumococcal strain was found to be associated with colonisation of that particular type in infants 7-24 months of age (Leino *et al.*, 2001). Shimada and colleagues (2002) gave evidence of household transmission of genetically similar strains of *S.pneumoniae* between siblings with concurrent or closely related episodes of AOM. More generally, a case-control study looking at risk factors for invasive pneumococcal disease (Nuorti *et al.*, 2000a) indicated that patients (especially 18-49 years of age) were three times as likely as control subjects to live in a household with children under the age of six who were in day care. Nuorti and colleagues, in the same study (2000a), showed also an association between low socioeconomic status (low educational level and low income, lack of health insurance) and pneumococcal disease. The relationship between family size as well as composition (number of children and adults in the family) and pneumococcal infection will be further investigated in Chapter 6 where the rate of infection by family size will be estimated using data from a longitudinal study of pneumococcal carriage in UK families.

Recent antibiotic treatment is also indicated as one of the causes of the increase in pneumococcal colonisation (Petrosillo *et al.*, 2002;Ghaffar *et al.*, 2002). This occurs through the generation of antibiotic resistant strains that survive the natural selection in the nasopharynx of colonised individuals and that are then likely to spread throughout the community.

Both active and passive smoking increase the risk of pneumococcal disease (Sung *et al.*, 1995;Nuorti *et al.*, 2000a;Iles *et al.*, 2001), as for other respiratory tract infections (Bogardus *et al.*, 2003). Nuorti and colleagues (2000a) found that the odds of invasive infection are four times higher for current smoker and that non-smokers, who were exposed to second hand smoke, experienced 2.5 times the odds of disease of non-smokers without such exposure. A clear dose-response relation with respect to the amount of smoking, the duration of passive exposure and the length of time since the cessation of smoking was also indicated in the study.

2.3.5 Immunity to *Streptococcus pneumoniae*

Although the nasopharynx is colonised frequently with pneumococci, the normal human respiratory tract opposes strong resistance to the development of symptomatic infection. Such resistance is not type specific and depends on anatomic and physiological characteristics of the host defence mechanisms (Austrian, 1984). Moreover, the activity of the spleen is known to prevent and limit the severity of *S.pneumoniae* infection, contributing in both the early stages of infection and also when the infection progresses enhancing the production of serotype-specific antibodies (Gillespie, 1989).

In contrast to this general resistance of the host, immunity to pneumococcal infection depends on both the natural (innate) and adaptive (acquired) immune mechanisms (Casal & Tarrago, 2003), which recognises elements of the surface structure of pneumococci and produces antibodies that may vary by the age of the host and by the invading serotype (Gillespie, 1989). Although historically studies of immunity to *S.pneumoniae* have focused on antibody to

pneumococcal capsular polysaccharide (CPS) as an essential element for the individual defence against a pneumococcal infection (MacLeod *et al.*, 1945;Heidelberger *et al.*, 1946;Zysk *et al.*, 2003), more recent works have shown that a variety of other antibodies are elicited by infection with encapsulated bacteria such as pneumococci (Bruyn *et al.*, 1992;Rapola *et al.*, 2000;Musher *et al.*, 2001;Rapola *et al.*, 2001a;Rapola *et al.*, 2001b). These antibodies are generated from encounters of the host defence mechanism with some of the most important virulence factors of the organism (section 2.2.3) such as pneumococcal surface protein A (PspA), pneumococcal surface adhesin A (PsaA), and pneumolysis (Ply). Unlike antibody to pneumococcal CPS, which are type-specific (Gillespie, 1989), antibody to surface proteins are common to all serotypes (Casal & Tarrago, 2003).

Naturally acquired immunity. Naturally acquired immunity to one or more pneumococcal types can be acquired passively from mother to child if the mother possessed such immunity in the form of immunoglobulin able to traverse the placenta (Austrian, 1984). This naturally acquired protection is serotype specific (Carvalho *et al.*, 1999) and wanes following birth, disappearing by the age of 7 months (Munoz FM *et al.*, 2002).

In older children and adults immunity is generated following episodes of pneumococcal carriage and is generally type specific although some evidence of cross-reaction between types have been shown (Coughlin *et al.*, 1998;Soininen *et al.*, 2001). Soininen and colleagues (2001) followed up 329 children prospectively during the first 2 years of life and found a significant increase in antibody production in children aged 12-18 months, when pneumococcal carriage and AOM rates are highest. Of these children, those who encountered types 11A or 14 pneumococci had significantly higher serum antibody titre of the homologous type than did children who had contact with heterologous serotypes. In contrast, antibodies to CPS 1, 19F and 23F correlated strongly with each other. Rapola and colleagues (2000) explored the relationship between the levels of IgG antibody to surface proteins and previous exposure to pneumococcal carriage in children and found that children who were exposed to pneumococci had a higher rise in antibody titres to PspA, PsaA and Ply. Anti-Ply,

in particular, was also found to be associated with the level of exposure (i.e. higher anti-Ply among children who had Pnc AOM than in healthy children colonised with Pnc).

The role of antibodies in protection against disease. Evidence of an inverse relationship between antibody levels (to both CPS and pneumolysin) and invasive pneumococcal disease is available (Musher *et al.*, 2001;Zysk *et al.*, 2003). Musher and colleagues (2001) explored in a cross sectional sample of middle aged adults (50-64 years old) the effect of antibody to pneumolysin on the development of pneumococcal disease and interestingly found that patients with bacteraemic pneumococcal pneumonia had significantly lower mean anti-pneumolysin IgG levels than patients with a non-bacteraemic condition. Furthermore, Musher and colleagues (1997) conducted a study in a military camp during an epidemic of pneumococcal pneumonia serotype 1 and found that 27.8% of those who were present at the camp at the time of the epidemic but who didn't develop the infection had IgG antibody to that specific type, whereas only 3.6% of controls had this antibody. A similar inverse relationship between antibody levels against CPS and incidence of invasive pneumococcal disease was observed by Zysk and colleagues (2003) who also investigated the antibody levels against some of the pneumococcal surface proteins and found no clear association with invasive pneumococcal disease. A number of studies have been performed (Virolainen *et al.*, 1996;Rapola *et al.*, 1997;Virolainen *et al.*, 2000;Rapola *et al.*, 2000;Rapola *et al.*, 2001a;Rapola *et al.*, 2001b;Rapola *et al.*, 2003) to investigate the relationship between antibody titres against pneumococcal surface proteins and exposure to pneumococci, but this relationship is still under discussion and no unanimous finding is available for the different proteins and the various pneumococcal related clinical conditions. An association between anti-PsaA antibodies and reduced involvement of *S.pneumoniae* in AOM was found by Rapola and colleagues (2001b) although only in infants older than 8 months of age. Similar findings have been found in mice, where vaccination with PsaA elicited protection against nasopharyngeal carriage of the pneumococcus and, in combination with PspA, also against Pnc bacteraemia and pulmonary Pnc infection (Briles *et al.*, 2000). However, more recent investigations (Rapola *et al.*, 2003) looked at whether anti-PsaA antibody would reduce the overall risk of pneumococcal AOM and/or of pneumococcal carriage and found a much more

complex interrelationship. A higher anti-PsaA concentration was found to predict a higher risk of pneumococcal carriage and of pneumococcal AOM (RR=1.51), whereas a higher anti-PsaA concentration at 12 and 18 months seemed to slightly decrease the risk of pneumococcal AOM (RR=0.94 and 0.88 respectively).

2.4 Pneumococcal vaccines

2.4.1 Polysaccharide vaccines (23-valent)

The currently available 23-valent polysaccharide pneumococcal vaccines (PPV), manufactured by both Aventis Pasteur MSD (Pneumovax@ II) and Wyeth-Lederle Pediatrics and Vaccines (Pnu-Immune@), include 23 purified capsular polysaccharide antigens of *S.pneumoniae* (serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F) which account for around 96% of pneumococcal isolates causing serious infections in England and Wales (George & Melegaro, 2001). These vaccines were licensed in the United States in 1983, and later marketed in Europe, replacing an earlier 14-valent formulation that was licensed in 1977 (ACIP, 1997). Pneumococcal capsular antigens induce a type-specific antibody response normally within 2-3 weeks in healthy young adults whereas the antibody response to most capsular types is generally poor or inconsistent in children aged <2 years (Douglas *et al.*, 1986;Koskela, 1986;Leinonen *et al.*, 1986). Therefore, these vaccines are licensed for immunization only of persons over the age of 2 years for whom the risk of contracting the pneumococcus is unusually high or dangerous (Figure 2.2) (Salisbury & Begg, 1996). Since July 2003 a pneumococcal immunisation programme for older healthy adults has also been introduced, partly as a result of the work performed in this thesis (Figure 2.2).

Re-immunisation with polysaccharide vaccine is not currently recommended in the UK except for people whose antibody levels are likely to have declined more rapidly (i.e. those with no spleen, with splenic dysfunction or with nephrotic syndrome). In these circumstances, another dose is recommended at 5-year intervals.

Figure 2.2 – Current PPV immunisation policy

Current PPV immunisation policy – at risk groups (Green Book)

Pneumococcal vaccine is already recommended for all those in whom pneumococcal infection is likely to be more common and/or serious. The at-risk groups, defined in paragraph 25.3 of the new pneumococcal chapter of Immunisation Against Infectious Disease 2003 (The Green Book available at www.doh.gov.uk/greenbook) are people with:

i. Asplenia or severe dysfunction of the spleen, including homozygous sickle cell disease and coeliac syndrome
ii. Chronic renal disease or nephrotic syndrome
iii. Chronic heart disease
iv. Chronic lung disease
v. Chronic liver disease including cirrhosis
vi. Diabetes mellitus
vii. Immunodeficiency or immunosuppression due to disease or treatment
viii. HIV infection at all stages.
ix. Cochlear implants

New immunisation policy – older adults

The new pneumococcal immunisation policy includes all adults aged 65 years and over who have not previously been immunised.

This policy is being introduced in England over the next 3 years, introducing younger cohorts each year. All people aged 80 years and over will be offered pneumococcal polysaccharide vaccine from 21st July 2003. They will be followed by all those 75 years and over from 1st April 2004 and all those 65 years and over from 1st April 2005.

The effectiveness of 23-valent polysaccharide vaccines has been assessed in various studies and the result seems to depend strongly on the study design used. On one hand case-control and retrospective cohort studies have indicated variable, but sometime considerable benefits in terms of vaccine efficacy against invasive disease among the elderly (Shapiro & Clemens, 1984;Sims *et al.*, 1988;Shapiro *et al.*, 1991;Butler *et al.*, 1993). On the other hand, meta-analyses based on randomised control trials show variable but sometimes very little protection of the vaccine against invasive pneumococcal disease in high or moderately high risk categories (Fine *et al.*, 1994;Hutchinson *et al.*, 1999;Moore *et al.*, 2000). Furthermore, the results appear to be strongly dependent on whether or not the studies included in the analysis are restricted to truly randomised trials or include quasi-randomised ones. Further insights on the efficacy of PPV will be presented in Chapter 4.

2.4.2 Conjugate vaccines

A heptavalent pneumococcal conjugate vaccine (PCV) has been registered in the USA and recommended by the American Academy of Paediatrics and the Advisory Committee on Immunisation Practices for universal use in children less than 24 months of age and also for high-risk children aged 2-5 years old (ACIP, 2000). In the latter setting, conjugate vaccination is followed by a polysaccharide booster in order to improve pneumococcal antibody titres in this age group. In the UK, the vaccine was licensed in 2001 and is now recommended to infants aged between 2 months and 5 years who are at increased risk.

Several studies have shown evidence of the direct effect of different formulations of the conjugate vaccines on the incidence of disease (invasive pneumococcal disease, pneumonia and acute otitis media) among vaccinated individuals (Table 2.3). Moreover, the vaccine reduces nasopharyngeal carriage of vaccine-type (VT) pneumococci (Table 2.4). In addition to individual protection against further development of pneumococcal disease, reduced colonisation of vaccinated individuals elicits protection against both pneumococcal colonisation and disease also among unvaccinated people (herd immunity). Some evidence of these indirect effects has already been presented for both pneumococcal carriage and disease (Table 2.5 and Table 2.6). In particular, Whitney and colleagues (2003) showed a decrease in the number of reported invasive pneumococcal disease cases (8%-32% in 20+ years of age) two years after the introduction of the conjugate vaccine. Whether this reduction is truly a consequence of the introduction of the conjugate vaccine, or if it simply follows the prevailing downward trend of invasive pneumococcal disease, is still under discussion and more post-vaccine surveillance data is necessary in the US and elsewhere in order to assess this.

Depending on the formulation, the conjugate vaccine covers 7 to a maximum of 11 pneumococcal serotypes. The proportion of disease caused by the serotypes contained in the 7-valent vaccine (the only one currently licensed) varies across different geographical areas, from 85% in the USA, to 60-70% in Europe and around 55% in Asia (Pelton *et al.*, 2003). As

a consequence of vaccination, the remaining non-vaccine types (NVT) may benefit from this selective immunological pressure. Replacement of VT with NVT in the nasopharyngeal *niche* of colonised individuals may thus occur causing a shift in the serotypes circulating in the population and, potentially, in disease. Serotype replacement has been observed in vaccinated as well as unvaccinated individuals colonised with pneumococci (Table 2.4 and Table 2.5). A switch in serotypes causing acute otitis media has been shown in the Finnish and Dutch trials (Eskola *et al.*, 2001;Veenhoven *et al.*, 2003), where AOM caused by non-vaccine types increased following the introduction of the conjugate vaccine (Table 2.3). So far, the effect of this mechanism on invasive disease remains unclear, although, recently, Kaplan and colleagues (2004) noted an increase of non-vaccine serotypes (i.e. 3, 15, 33) causing invasive disease in American children 2 years of age or less. Also, Brueggemann and colleagues (2003) confirmed the results found in the early 1990s by Smith and colleagues (1993) who derived the invasiveness of the different serotypes comparing carriage data to disease data. Both the studies showed that certain NVT (i.e.1, 7) have a high invasive capacity, although most do not. This suggests the potential for serotype replacement to lead to replacement in invasive disease as well, al least for some serotypes.

Bacterial replacement as a consequence of vaccination might also include other species, which, similarly to NVT dynamics, can invade the colonisation space that was occupied by VT in the pre-vaccination period. Veenhoven and colleagues (2003) showed a significant increase in *Staphylococcus aureus*-related acute otitis media after vaccination, though the numbers of middle-ear fluid cultures of untypable *H.influenzae*, *M.catarralis*, group A streptococci and *P.aeruginosa* did not differ between vaccine and control groups. Moreover, a negative correlation has been detected for co-colonisation of *S.aureus* and vaccine-type pneumococci (OR 0.68, 0.48-0.94), but not for *S.aureus* and non-vaccine serotypes (Bogaert *et al.*, 2004b). These findings suggest that a natural competition between colonisation with vaccine-type pneumococci and *S.aureus* may well exist, and that this might explain the increase in *S.aureus*-related otitis media after vaccination shown in Vennhoven's study.

Direct and indirect effects of vaccines are both crucial elements to considering the changes to national immunisation policies. The direct effects (i.e. reduction in carriage and, thus, disease in vaccinated individuals) are usually available as a result of properly designed studies and surveillance data in time with the launch of the vaccine. Indirect effects are usually only visible after the introduction of the vaccine when, in fact, the policy has already been implemented. Nevertheless, their impact can be substantial when evaluating a vaccination policy, both in terms of health gains as well as in terms of costs. In the following work we will use modelling techniques in order to take these effects into account.

Table 2.3 - Summary table on the direct effect of PCV on pneumococcal disease

References	Study area	Study type	Vaccine type	Age at vaccination	IPD	Pneumonia	Otitis Media
Whitney *et al.*(2003)	USA	SURV.	CRM-7	2,4,6,12-15 mths	VT: 78%; CRT: 50% NVT: -27%	-	-
O'Brien *et al.*(2003)	American Indian	Group RCT	CRM-7	2,4,6,12-15 mths	Any IPD: 52%; VT: 82.6%	-	-
Veenhoven *et al.*(2003)	The Netherlands	RCT	CRM-7 + PPSV-23	1,7 mths	-	-	Any type = 11%; VT reduced NVT increased
Singleton *et al.*(2002)	Alaska	SURV.	CRM-7	2,4,6,12-15 mths	Comparing 2001 vs. 1999/2000 data: VT: 62-83% (<2 yrs), 42-71% (2-4 yrs); NVT equal	-	-
Black *et al.*(2001)	USA	SURV.	CRM-7	2,4,6,12-15 mths	VT: 62% (<5 yrs), 58% (<2), 87% (<1); NVT equal	9-18%	-
Eskola *et al.*(2001)	Finland	RCT	CRM-7	2,4,6,12 mths	-	-	Any type: 6-9%; Pnc AOM: 34%; VT=57%; NVT=-33%
Kilpi *et al.*(2003)	Finland	RCT	OMPC	2,4,6,12 mths	-	-	Any type=25%; VT=56%; CRT=-5%; NVT=-27%
Dagan *et al.*(2001)	Israel	RCT	CRM-9	12-35 mths (DCC)	-	16%*	Any type=17%
Fireman *et al.*(2003)	USA	RCT	CRM-7	2,4,6,12-15 mths	-	-	Any type=7.8%
Klugman *et al.*(2003)	South Africa	RCT	CRM197	6,10,14 wks	Any IPD: 50%; VT=72%; NVT=-44% CRT=41%	Radiological confirmed first episode of pneumonia 17%	-
Black *et al.*(2002)	USA	RCT	CRM-7	2,4,6,12-15 mths	-	all clin pn=6%; clin pn + radiog =8.9%; clin pn + perih find=11.1%; clin pn+ pos film=17.7%	-
Black *et al.*(2000)	USA	RCT	CRM-7	2,4,6,12-15 mths	Any IPD: 89%; VT=94%;	-	Any type=6.4-12.3%; PncAOM=65-67%
Kaplan *et al.*(2004)	USA	SURV.	CRM-7	2,4,6,12-15 mths	Comparing 2002 vs 1994-2000 data: VT: 77% NVT: -66%		

*SURV.=surveillance, RCT=randomised controlled trial, CRT=cross-recative serotypes; VT=serotypes contained in the 7-valent vaccine, NVT=non-vaccine serotypes, DCC=day-care centre, *lower respiratory problems.*

Table 2.4 – Summary table on the direct effect of PCV on pneumococcal carriage

References	Study area	Study type	Vaccine type	Age at vaccination	Carriage of vaccine types (VT) among vaccinees	Carriage of non-vaccine types (NVT) among vaccinees
Dagan *et al.*(2002)	Israel	RCT	CRM-9	12-35 mths (DCC)	50% reduction (13% vs. 21%)	28% increase (44% vs. 34%)
Yeh *et al.*(2003)	Southern California	RCT	PCV-OMP	2,4,6,12 mths	52% reduction, n.s. (10.3% vs. 21.4% in controls at 13 months of age)	-
Palmu *et al.*(2002)	Finland	FUP	CRM-7	2,4,6,12 mths	Reduced (8.5% vs. 13.6%, RR=0.62)	Increased (4.7% vs. 2.3%, RR=2.1)[c]
Mbelle *et al.*(1999)	Soweto, South Africa	RCT	CRM-9	6,10,14 wks	Reduced (18% vs. 36% at age 9 mths)	Increased (36% vs. 24% at age 9 mths)
Dagan *et al.*(1997)	Israel	RCT	D-4, T-4[a]	2,4,6 mths	Reduced (0% (D-4) 13% (T-4) vs. 29% (control) at age 13 mths)	-
Dagan *et al.*(1996a)	Israel	RCT	OMPC-7[b]	12,15,18 mths	Reduced (1 dose: 14% vs. 21%, 2 doses: 11% vs. 25% after 1 yr)	Increased after one yr (1 dose: 38% vs. 15%; 2 doses: 32% vs. 22%)
Obaro *et al.*(1996a)	Gambia	FUP	CRM-5	2,3,4 mths	Reduced (3 doses: OR= 0.11, 2 doses: OR=0.22)	Increased (3 doses: OR= 4.51, 2 doses: OR=0.65**)

*[a]4 polysaccharide conjugated to diphtheria toxoid (D-4) or tetanus toxoid (T-4); [b]7 polisaccharide conjugated with the outer membrane protein complex of N.meningitidis type B; [c]cross-reactive serotypes (6A, 9N, 18B, 19A, 23A); ** 95%CI overlapping 1; DCC=day-care centre.*

Table 2.5 - Summary table on the indirect effect of PCV on pneumococcal carriage

References	Study area	Study type	Vaccine type	Objective	Overall Pnc carriage	VT Pnc carriage	NVT Pnc carriage
Givon-lavi *et al.*(2003)	Israel	RCT	CRM-9	HI among younger siblings of vaccinees attending DCC	-	36% reduction, p=0.017 (34% vs. 21%)	46% increase, n.s. (13% vs. 19%)
Watt *et al.*(2002)	American Indian	NP study	CRM-7	HI in adult family members (18+ yrs)	Equal (14.9% vs. 14.3% in controls, n.s.)	Reduced (2.0 vs. 4.2%, p<0.01)	Increased (11.2 vs. 8.1%, p<0.05)
O'Brien *et al.*(2002)	American Indian	NP study	CRM-7	HI in children living in the same h/hold (< 6 yrs)	Equal (70.6% vs. 63.8% in those living with controls, RR=1.1)	Reduced (40% vs. 49%, RR=0.8)	Increased (60% vs. 49%, RR=1.2)

NP=nasopharyngeal; RCT=randomised controlled trial; HI=herd immunity; DCC=day-care centre.

Table 2.6 - Summary table on the indirect effect of PCV on invasive pneumococcal disease.

References	Study area	Study type	Vaccine type	Objective	IPD
Whitney *et al.*(2003)	USA	SURV.	CRM-7	Effects on IPD rates among adults	Reduced: 32% (20-39 yrs); 8% (40-64 yrs); 18% (65+ yrs)
Moulton *et al.*(2002)	American Indian	SURV.	CRM-7	HI among communities residents	Equal
Singleton *et al.*(2002)	Alaska	SURV.	CRM-7	Comparison with 1999-2000 data	Equal (VT: from 57% in 1999/2000 to 56% in 2001)
Kaplan *et al.*(2004)	USA	SURV.	CRM-7	Effects on hospitalised IPD children (3-4 years of age)	Equal

SURV.=surveillance

2.5 Surveillance of pneumococcal disease in England and Wales

The uncertainties with regards to the long-term effect of the introduction of new formulations of pneumococcal vaccines makes the availability of surveillance data even more crucial than in normal circumstances. A number of data sources are available and, although none of them can be considered complete and exhaustive, they all facilitate the monitoring and assessment of potential changes in pneumococcal disease trends. However, whereas for invasive pneumococcal disease the surveillance system in place is based on aetiologically confirmed pneumococcal diseased patients, the monitoring of less severe non-invasive pneumococcal cases usually relies upon clinical diagnosis. For instance, the Royal College of General Practitioners (RCGP) sentinel surveillance system reports the clinical manifestation for which the visit is required (i.e. pneumonia and acute otitis media) but not the related organism. Hospital admissions are also available for the different pneumococcal related condition and can be used also to ascertain the costs related to the most severe conditions. Again, discharge diagnoses are often clinical rather than microbiologically based.

Although the management and use of each specific data source will be fully described in Chapter 3, the following paragraphs aim to give a brief introduction on the data that are available to gain insights into the epidemiology of pneumococcal disease.

2.5.1 Laboratory reports

The Health Protection Agency Communicable Disease Surveillance Centre's (CDSC) national laboratory reporting scheme is the main data source for the ascertainment of invasive pneumococcal disease in England and Wales (Miller *et al.*, 2000). This is based on voluntary weekly reports to CDSC of all clinically significant bacterial isolates from blood, cerebrospinal fluid (CSF) and other sterile sites from public health and non-public health laboratories around England and Wales. Each record corresponds to an individual episode of illness and contains information such as: patient's date of birth, sex, age, reporting laboratory, and nature of specimen or specimens from which the organism was isolated. When the

bacterium is isolated from the CSF, the patient is recorded as a meningitis case. Sometimes additional information on associated clinical features, during and at the end of the episode, and on antibiotic susceptibility is also included.

A second data source consists of IPD isolates referred for serotyping to the Respiratory and Systemic Infection Laboratory (RSIL) at the Specialist and Reference Microbiology Division of the Health Protection Agency. From 1996 all laboratories reporting an invasive pneumococcal infection in children less than 6 years of age to the national surveillance system were asked to send to RSIL the isolate from that patient for serotyping, if they had not already done so. As not all the isolates sent to RSIL for serotyping are reported also to CDSC, and *vice versa* the two databases were therefore reconciled in 1996, matching on date of birth, date of specimen taken, sex, source of laboratory, name of patient or Soundex code when the name was not available. Moreover, the Antibiotic Reference Unit (ARU) at the Specialist and Reference Microbiology Division routinely performs antibiotic sensitivity testing on the isolates referred to RSIL.

2.5.2 Notifications

Clinicians have been required by statute to notify the proper officer of the local authority (usually the Consultant in Communicable Disease Control) cases of pneumococcal meningitis since 1968 (McCormick, 1993). Clinically diagnosed cases of pneumococcal meningitis are reported on a weekly basis to regional health authorities and data are collated at CDSC and published in the Communicable Disease Report.

2.5.3 Consultation to General Practice

The Royal College of General Practitioners (RCGP) set up a sentinel surveillance programme using a representative sample (currently 69 practices) of the practitioners throughout England and Wales in 1967 (Fleming, 1999). The system, which evolved from the Epidemic Observation Unit of the College of General Practitioners set up in 1953, provides weekly data

on diagnosis (now recorded with the ICD-9 coding system), age, and sex of the patient who consults the GP. Each report is based on a new episode of illness although ongoing consultations are also reported.

2.5.4 Hospital Episode Statistics

A further source of information for pneumococcal disease, which also includes more information on co-morbidities, is the Hospital Episode Statistics (HES) (http://www.dh.gov.uk/Home/fs/en). This is a computerised hospital discharge database that collates output from all National Health Service hospitals in England. It contains information on individual episodes of illness, together with patient's details (age, date of birth, postcode, sex), clinical conditions, number of days spent in the hospital and admissions to Intensive Care Unit (ICU). For each record, seven diagnostic fields are available, allowing co-morbidities to be recorded. Since April 1995 the tenth revision of the International Classification of Disease (ICD-10) has been adopted for coding discharge diagnosis. Before that time the ICD-9 version of the code was used.

2.5.5 Deaths

Doctors have been required to certify the cause of death for patients under their care since the early 1840s (Rooney & Devis, 1996). The certifying doctor is required to explicitly state the condition that led directly to death in Part I of the certificate, whereas the disease or condition, which started the sequence, is reported in the lowest line (what is defined the underlying cause of death). All certified deaths are notified to the Office for National Statistics (ONS), and coded according to ICD codes 9th revision (ICD-9) until 1999 and 10th revision for 2000 data and onward.

2.6 Discussion

This chapter presented an overview of the pneumococcus, the pneumococcal vaccines and the surveillance systems that are available to monitor the incidence of pneumococcal disease in the UK. These aspects represent the necessary background that is needed in order to investigate the epidemiology of the bacterium, the characteristics of its transmission dynamics in the population and the potential effects of different vaccination policies. Using the surveillance systems that are available for the UK, in the following chapter (Chapter 3) the epidemiology of *S.pneumoniae* infection in England and Wales will be described and the current burden of pneumococcal disease will be estimated.

CHAPTER 3 - THE EPIDEMIOLOGY OF PNEUMOCOCCAL DISEASE IN ENGLAND AND WALES

3.1 Aims

- To describe and compare available surveillance systems for pneumococcal disease;
- To describe the epidemiology of pneumococcal disease in children and in the elderly;
- To describe changes in the serotypes distribution of pneumococcal disease;
- To investigate the antibiotic susceptibility patterns of pneumococcal disease cases over the years;
- To estimate the overall burden of pneumococcal disease in England and Wales.

3.2 Introduction

In this chapter the epidemiology of pneumococcal disease is described and the current burden of disease in England and Wales is estimated. Reliable surveillance systems are required in order to monitor incidence and trends in infectious diseases. Surveillance systems are used to inform policy decision makers about possible control measures and also to ascertain the impact of specific interventions, such as vaccination, once they have been put in place. As described in the previous chapter, two pneumococcal vaccines are currently available and recommended in the UK although a number of open questions are still threatening the overall effectiveness of the vaccination programmes. In particular, uncertainties related to the indirect and long-term effects of new formulations of pneumococcal conjugate vaccines (i.e. herd

immunity and serotype replacement) - discussed in section 2.4.2 - require a comprehensive and well planned surveillance system which would enable the ascertainment of changes in the overall morbidity and mortality due to *S.pneumoniae* from the pre to the post vaccination era.

A number of data sources are available and taken together they facilitate the monitoring and assessment of potential changes in pneumococcal disease trends. Whereas for invasive pneumococcal disease the surveillance system in place is based on laboratory reports of microbiologically confirmed cases of pneumococcal disease, less severe non-invasive pneumococcal conditions (i.e. pneumonia and acute otitis media) are monitored using a surveillance system (RCGP) that is based on vague clinical definitions that are unlikely to be investigated microbiologically. However, hospital admissions (HES) are also available for different pneumococcal related conditions and can also be used to ascertain the overall burden of disease and the associated costs.

3.3 Method

3.3.1 Sources of data

The sources of data for pneumococcal diseases have been presented in Chapter 2 (section 2.5). In the following paragraphs, the management of the data will be described.

Laboratory reports. Line listings of cases of laboratory confirmed invasive pneumococcal disease reported from laboratories in England and Wales from January 1990 to December 2000 was extracted. Since 1996 the data were downloaded from the newly reconciled enhanced surveillance system of invasive pneumococcal disease (CDSC/RSIL) which is the most complete dataset for IPD in England and Wales containing information on serotype as well as antimicrobial susceptibility information for around 50% of the cases (George & Melegaro, 2001). IPD cases were those for which pneumococci were isolated in the blood, CSF or other normally sterile body fluids. Only strictly invasive infections were extracted though some non-invasive cases are also recorded in the system. Pneumococcal meningitis

cases were defined where the organism was isolated from the CSF or when the diagnosis of "pneumococcal meningitis" was specifically reported in the patient's record. The extracted data included age, sex, earliest specimen date, serotype (when available), antimicrobial susceptibility information (penicillin and erythromycin), region and method of confirmation.

Hospital Episode Statistics (HES). From HES all hospital admissions reporting one of the pneumococcal related ICD-10 codes (Table 3.1) in any of the seven diagnostic fields were extracted. This included strictly IPD codes (pneumococcal meningitis and septicaemia), pneumococcal pneumonia (under which both IPD and non-IPD can be recorded) as well as non-invasive codes such as otitis media and lobar or unspecified pneumonia. Admissions due to lobar pneumonia, organism unspecified (J181), were extracted as pneumococcus is considered one of the major cause of lobar pneumonia, especially in children (Djuretic *et al.*, 1998). In the former ICD-9 coding system a unique code (481) was used for both lobar pneumonia, organism unspecified, and pneumococcal pneumonia (Djuretic *et al.*, 1998;Miller *et al.*, 2000).

Table 3.1 - International classification of diseases codes for pneumococcal disease

Definition	**ICD-9 code**	**ICD-10 code**
Pneumococcal meningitis	3201	G001
Pneumococcal septicaemia	0382	A403
Pneumococcal pneumonia	481	J13X
Lobar pneumonia, organism unspecified	481	J181
S.pneumoniae as the cause of the disease	410	B953
Non-Suppurative otitis media	3810-3814	H650-H659
Suppurative and unspecified otitis media	3820-3829	H660-H669
Otitis media in diseases classified elsewhere	n.a.	H670-H678

n.a. = no equivalent ICD-9 code was available

The period between April 1995 and March 2000 was considered (HES financial year goes from April to March). As in HES each episode of patient care under a consultant is recorded, and as a patient may have several different episodes during a single hospital stay (i.e. change of consultants, unit, etc.), the records were linked together through the personal identifiers

(date of birth, sex and district health authority of the hospital (DHAtreat)) and the admission date, which should remain the same, and the last episode of each patient hospitalisation was retained. When it was not possible to link different episodes of the same patient's admission, due to inappropriate date coding, further investigations were required. Moreover, as there may also be duplicates in the data, the following criteria were followed in order to minimise the number of episodes from the same patients:

a) A duplicate record was deleted when patient date of birth, sex, postcode, admission date and date episode began and ended were the same;
b) Any multiple episodes were identified ("epiorder">1) and when the patient date of birth, sex, DHAtreat and admission date were the same only the record with the latest episode end date was retained;
c) Matching on date of birth, sex, date of admission, and DHAtreat identified any multiple episodes that had not been linked. All matching records were ordered by date of episode. If the dates of the episodes overlapped the record with the latest episode end was retained, and other records were deleted.

Once the data were cleaned, each hospitalisation was recorded according to the reported pneumococcal code and to whether this code appeared in the first diagnostic field, in the first three or in the last three fields. We assumed that more important clinical conditions were recorded in the first diagnostic field. In case more than one pneumococcal code was present for a patient, the most severe code was considered first. The following order of importance was thus followed: G001, A403, J13, B953, J181. Otitis media hospitalisations were treated separately and were available only for the period 1999-2000.

GP Consultations. The weekly number of consultations to general practitioners for a diagnosis of either pneumonia/pneumonitis or acute otitis media and population at risk was obtained from the Royal College of General Practitioners (RCGP) Weekly Returns System. The bi-weekly number of pneumonia and AOM was calculated for the period 1996-2000 and used as an outcome variable in a multivariate regression analysis with the aim of investigating

the underlying aetiologies of GP consultations for pneumonia and AOM and, thus, the proportion of these attributable to *S.pneumoniae*. The details of the analysis are reported below (Section 3.3.2.1).

Moreover, additional and more detailed information on patients attending the GP practices was available from the Morbidity Survey of General Practices Fourth Edition (MSGP4), which is a one-year prospective survey of around 500,000 patients attending GP practices (McCormick *et al.*, 1995). This database contains information on people attending the practices in the survey, such as socio-economic status, details on family composition, individual characteristics (i.e. smoking status) and the history of the patient's health status during the year of the survey.

Notifications. The total number of pneumococcal meningitis cases diagnosed and notified by clinicians and reported to CDSC was extracted for the period 1995-2000. Figures were compared to the overall numbers reported by laboratories around England and Wales to CDSC/RSIL enhanced surveillance system.

3.3.2 Data analysis

3.3.2.1 Comparison of data sources

The total number of pneumococcal confirmed cases identified by laboratory reports, notifications and HES for the period 1995-2000 (the last year that was available at the time of the analysis) was derived and comparisons were made between the data sources. The seasonal patterns were investigated from both laboratory reports and hospitalisations data.

Multiple linear regression analysis was used, following the technique developed by Ryan and colleagues (1996), to ascertain the underlying aetiologies of pneumonia and acute otitis media GP consultations and to estimate the proportion attributable to *S.pneumoniae* infection. The observed seasonality in agents that could potentially cause pneumonia and AOM was compared to the number of consultations reported for the two clinical outcomes over the same

time period. The weekly number of consultations (RCGP) for the period 1996-2000 was used as the dependent variable of the regression. The independent variables were the weekly number of national laboratory reports for the following agents: *Streptococcus pneumoniae*, *Haemophilus influenzae*, Adenovirus, Influenza A (Flu A), Influenza B (Flu B), *Klebsiella pneumonia*, *Legionella pneumophila*, *Moraxella catarrahlis*. *Mycoplasma pneumonia*, Parainfluenza, *Pneumocistis carinii*, Rhinovirus, RSV, *Chlamydia pneumonia* and *Chlamydia pisittaci*.

The formula for calculating the expected number of GP consultation for pneumonia (and similarly AOM) Y_j in a 2-week period j is:

$$Y_j = C + \sum \alpha_i L_{ij} \qquad 3.1$$

Where L_{ij} is the number of laboratory reports for pathogen i in the 2-week period j, α_i is the regression coefficient for organism i used to estimate the number of GP consultations associated with each organism, and C is a constant representing the background number of GP consultations for pneumonia associated with other infectious or non-infectious causes of clinically suspected pneumococcal disease.

As the age-specific weekly number of GP consultations was not available, patients of all ages were combined, as well as laboratory reports. A backward stepwise regression was performed using STATA 6.0. This technique is based on a variable selection procedure in which all variables are entered into the equation and then sequentially removed if non significant (p-value>0.05). The importance of two-way interaction terms for the explanation of the dependent variables was also investigated, assessing the significance ($p<0.01$) of each interaction term between the organisms in the final model. The validity of the model was assessed (R^2) and the impact of changes in the model specification was investigated.

3.3.2.2. Analysis of epidemiological data

Age-specific incidences of laboratory confirmed IPD was calculated using ONS population estimates for the appropriate years and age groups. Similarly, hospitalisation rates were derived separately for each pneumococcal related ICD-10 code and, also, for any pneumococcal confirmed hospitalisations, using ONS population estimates for England.

The serotype distribution of IPD cases was derived for each year from 1996 to 2000 examining the isolate characteristics and identifying the most common 15 serotypes in the following age groups: <5 years, 5-64 years and 65+. Less common serotypes were grouped together. The proportions of invasive infections that are caused by the serotypes contained in the different formulations of pneumococcal conjugate and polysaccharide vaccines were estimated for different age groups and for each year. Moreover, for each isolate, information on the susceptibility to penicillin and erythromycin was also derived and resistance patterns were examined for the most prevalent types and for the different age groups.

The number of patients that died during their hospital admission was derived. Case-fatality ratios (CFR) from 1995/96 to 1999/2000 were estimated by dividing the number of deaths by the number of pneumococcal disease cases admitted to the hospital. Due to the presence of other serious co-morbidities conditions in many patients (especially the elderly) hospitalised with pneumococcal codes, it was not possible to ascertain with confidence from the data whether the patient had died because of the pneumococcal infection or, simply, with a pneumococcal infection. For this reason we estimated CFR for patients reporting a pneumococcal code in the first diagnostic code, in the first three or in any of the seven diagnostic fields. Considering that the first diagnosis is more likely to report the underlying cause of the hospitalisation, we assumed that CFR calculated on the first diagnosis only were more likely to be related to *S.pneumoniae* infection. From ONS, the number of pneumococcal related deaths (i.e. pneumococcal code as the underlying cause of death) were also obtained and CFR were estimated dividing these figures by the number of laboratory reports. Although, in fact, vital status information is available for some of the IPD cases reported from

the laboratories, these data are far from being complete (3% in 2000 data) and hence could not be used for deriving pneumococcal specific mortality.

Average age-specific episode and consultation rates for community-acquired pneumonia and acute otitis media were estimated using MSGP4 data and compared to the rates provided by RCGP. Moreover, from MSGP4 data, episode rates of both CAP and AOM due to pneumococcal infection were also derived for high and low-risk individuals, stratifying the patients according to whether their clinical record reported one of the following chronic medical conditions: diabetes mellitus, chronic renal, hepatic, or pulmonary disease, alcoholism, or neoplastic disease, chronic immunosuppression. These represent the high-risk group for which the polysaccharide pneumococcal vaccine has been in the past and is currently recommended (Chapter 2).

3.4 Results

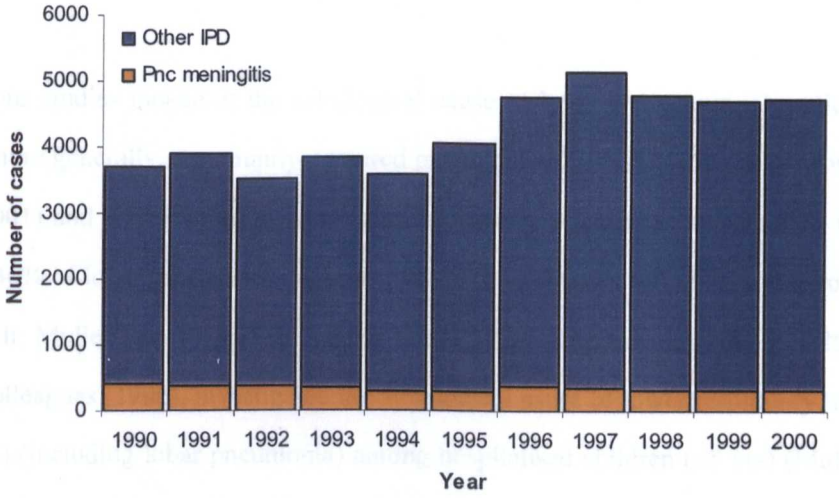
3.4.1 Comparisons of data sources

From CDSC/RSIL the number of laboratory reports for each year since 1990 was obtained and showed an increase in the annual figure in 1996 when the enhanced surveillance system was implemented (Figure 3.1). Since then, an annual average of around 4700 IPD cases had been reported. Of these, an average of 343 were identified as cases of pneumococcal meningitis (pneumococci isolated from the CSF) whereas the remaining isolates were obtained from bacteraemic patients with pneumococcus isolated from the blood or other sterile body fluids.

More cases of pneumococcal meningitis were identified in HES than in the laboratory reports and notification system each year (Table 3.2). This suggests that the latter systems may underestimate the true incidence of pneumococcal meningitis. Similarly, the overall number of invasive pneumococcal isolates reported from the laboratories around England and Wales was lower than the number of hospital admissions due to confirmed pneumococcal infection

(ICD-10 codes: G001, A403, J13, B953) for the same years. Although this may again suggest that laboratories are underreporting the number of IPD cases to the national surveillance system, it may also highlight the non-invasive nature of codes J13 and B953 which, differently from the other codes (G001, A403), do not necessarily imply that pneumococci have been isolated from a sterile body fluids (which represents the criterion for extraction of invasive pneumococcal isolates from laboratory reports).

Figure 3.1 – Cases of pneumococcal meningitis and other IPD in England and Wales (1990-2000).



Source: National enhanced surveillance of pneumococcal disease (CDSC/RSIL).

The presence of an epidemic cycle was assessed using weekly laboratory reports of IPD and hospitalisations for confirmed pneumococcal infection. A marked seasonal pattern in the presentation of IPD with preponderance in the winter months was observed. Figure 3.2 notes the number of cases reported from laboratories around England and Wales by week of *earliest specimen date* over the period 1995-2000. Reported IPD cases reach a low during August and peak in December and January when reporting rates are 3-5 times higher. Although these reports regard most severe cases of pneumococcal infection (the invasive ones), they probably represent just a small proportion of the true burden of pneumococcal disease present both in the community and in the hospital. The seasonal changes in disease presentation observed here, however, may be correlated to the more intense circulation of respiratory viruses during

the same period of the year, and also appear to be reflected in non-IPD admissions to hospitals and consultations in Primary Care. Figure 3.3 shows a comparison between laboratory weekly reports of IPD and hospitalisations due to all pneumococcal confirmed infection and also admissions with a diagnosis of lobar pneumonia, organism unspecified. The almost overlapping seasonal pattern observed when considering all confirmed pneumococcus-related patients suggests that hospital episodes with an ICD-10 code mentioning *S.pneumoniae* are an accurate reflection of IPD incidence as reported in the national enhanced surveillance system (CDSC/RSIL). Moreover, a similar seasonal pattern characterises also lobar pneumonia admissions though the numbers are much higher.

Previous studies looked at the aetiological cause of lobar pneumonia (Djuretic *et al.*, 1998) and, more generally, community-acquired pneumonia (CAP) requiring hospitalisation (Lim *et al.*, 2001) and showed that the proportion caused by pneumococcal infection is high, going from 46% of lobar (pneumococcal) pneumonia (ICD-9 code: 481) in children to 48% of CAP in adult. Muller-Pebody and colleagues (2002), following the technique developed by Ryan and colleagues (1996), investigated the aetiological cause of lower respiratory tract infections (LRTI) (including lobar pneumonia) among hospitalised children (<5 yrs) (Muller-Pebody *et al.*, 2002) and elderly patients (65+ yrs) (Muller-Pebody personal communication) and found that, respectively, 42% and 19.8% of unspecified hospitalisations for LRTI were attributable to *S.pneumoniae.*

Table 3.2 – Number of laboratory reports, notifications and hospitalisations in England and Wales (1995-2000).

	Laboratory reports (CDSC/RSIL)			Notification (NOIDS)	Hospitalisations (HES)[a]					
Year	Pnc meningitis	Other IPD	All IPD	Pnc meningitis	Pnc meningitis (G001) [1]	Pnc septicaemia (A403) [2]	*S.pneumoniae* as the cause of the disease (B953) [3]	Pnc pneumonia (J13) [4]	Pneumococcal confirmed cases [1+2+3+4]	Lobar pneumonia, organism unspecified (J181)
1995	281	3768	4049	241	488	635	874	4229	6226	33578
1996	394	4377	4771	297	494	639	1181	3214	5528	31105
1997	355	4804	5159	300	522	675	1197	3024	5418	36250
1998	321	4462	4783	243	483	666	1293	2782	5224	40884
1999	334	4358	4692	237	467	726	1340	2515	5048	40463
2000	314	4421	4735	218	500	609	1037	2069	4214	32377

[a]*HES records hospitalisations in England. HES 2000 data is provisional, estimated on the figures for the first trimester. NOIDS=Notifications for Infectious Diseases*

Figure 3.2 – Weekly number of invasive *S.pneumoniae* isolates in England and Wales reported to the national laboratory surveillance system (1995-2000)

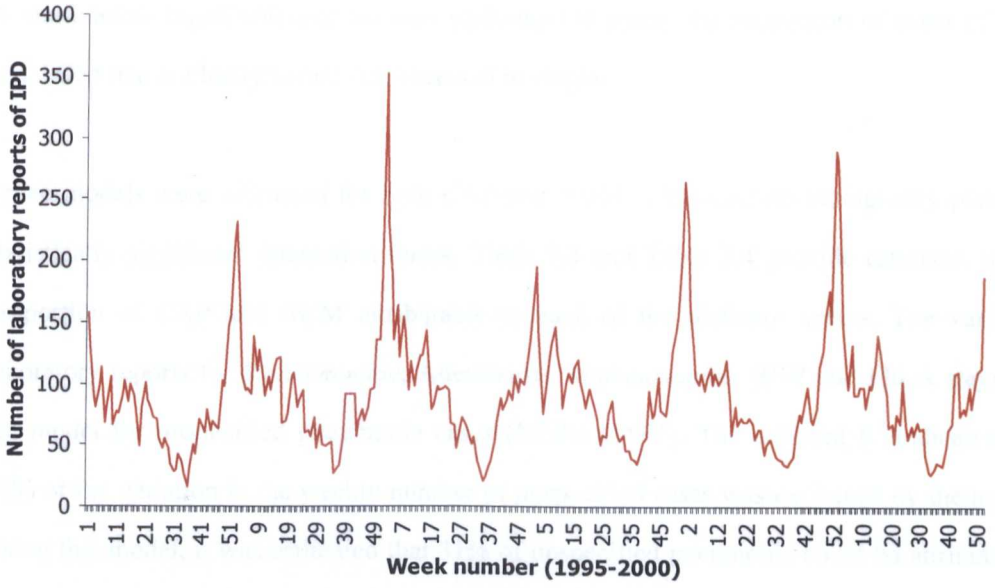
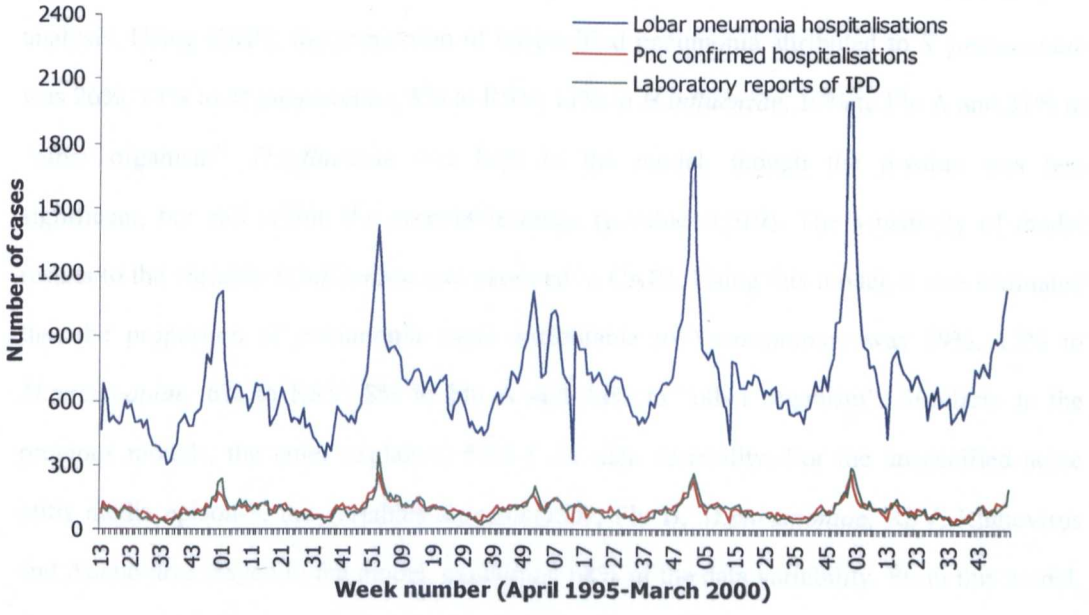


Figure 3.3 – Comparison of weekly reports of pneumococcal disease from the national laboratory surveillance system and from hospital admissions (1995-2000).



Pnc confirmed hospitalisations include the following ICD-10 codes: G001, A403, J13, B953 reported in any of the seven diagnostic fields. ICD-10 code for lobar pneumonia: J181.

3.4.2 Multiple regression analysis of GP consultations

A multivariate regression analysis was performed to assess the proportion of cases of CAP and AOM that are likely to be pneumococcal in origin.

Three models were estimated for both CAP and AOM. We found no biologically plausible statistically significant interaction terms. Table 3.3 and Table 3.4 provide estimates of the proportion of CAP and AOM attributable to each of the different agents. The variables laboratory reports for *S.pneumoniae*, Adenovirus, *M.pneumoniae*, RSV and Flu A stayed in the model for unspecified pneumonia cases (Model CAP1). The adjusted R^2 indicates that 67% of the variation in the weekly number of unspecified cases was explained by the model. Using this model, it was estimated that 31% of unspecified pneumonia could be attributed to *S. pneumoniae*, 38% to Adenovirus, 17% to *M.pneumoniae*, 6% to RSV and 8% to Flu A. A slightly more adequate fit (R^2=68%) was achieved by model CAP2, where the variable Adenovirus was dropped from the model and "other organism" was added to consider all the other possible infectious and non infectious causes of pneumonia that were not included in the analysis. Using CAP2, the proportion of unspecified pneumonia attributed to *S. pneumoniae* was 26%, 14% to *M.pneumoniae*, 8% to RSV, 11% to *H.influenzae*, 10% to Flu A and 31% to "other organism". *H.influenzae* was kept in the model, though the p-value was less significant, but still within the acceptable range (p-value=0.019). The sensitivity of model results to the variable *H.infleunzae* was assessed in CAP3. Using this model, it was estimated that the proportion of pneumonia cases attributable to *S.pneumoniae* was 29%, 12% to *M.pneumoniae,* 6% to RSV, 8% to Flu A and 44% to "other organism". Similarly to the previous models, the latter explained 67% f the data variability. For the unspecified acute otitis media episodes, the variables *S.pneumoniae*, Flu B, *M.pneumoniae*, RSV, Rhinovirus and Adenovirus stayed in the model, explaining 68% of the data variability. From this model, *S.pneumoniae* was estimated to cause 23% of AOM episodes, 4% were due to Flu B, 12% to *M.pneumoniae*, 8% to RSV, 18% to Rhinovirus and 36% to Adenovirus. Dropping Adenovirus from the model reduced the fit to 63% and 58% when the variable "other organism" was, respectively, included and excluded from the model specification.

In summary, from the six models just described, *S.pneumoniae* was estimated to cause from 26% [95%CI: 10-37%] to 31% [95%CI: 21-39%] of pneumonia consultations, whereas from 23% [95%CI: 14-29%] to 42% [95%CI: 36-47%] of AOM consultations. Figure 3.4 and Figure 3.5 show the observed and estimated seasonal patterns and the contribution of each pathogen.

Although not much variation was found in the proportion of CAP attributable to pneumococcal infection in the three models, *CAP2* was the one that showed the best fit (highest adjusted R-square) and, consequently, was chosen as our final model. The proportion of GP consultations for CAP attributable to *S.pneumoniae* was thus assumed to be 26%. Similarly, the proportion of AOM attributable to pneumococcus was assumed to be 23% according to model *AOM1,* being this the model with the best fit (adjusted R-square equal to 70%). These results will be used in section 3.4.3.5 to derive the pneumococcal age-specific consultation rates to the general practitioner.

Table 3.3 – Estimation of the proportion of unspecified CAP attributable to specific pathogens.

Pathogen	Model CAP1*	Model CAP2 – Final model	Model CAP3
S.pneumoniae	31%	26%	29%
Adenovirus	38%	-	-
M.pneumoniae	17%	14%	12%
RSV	6%	8%	6%
H influenzae	-	11%	-
Flu A	8%	10%	8%
Other organism	-	31%	44%
Adjusted R^2	67%	68%	67%

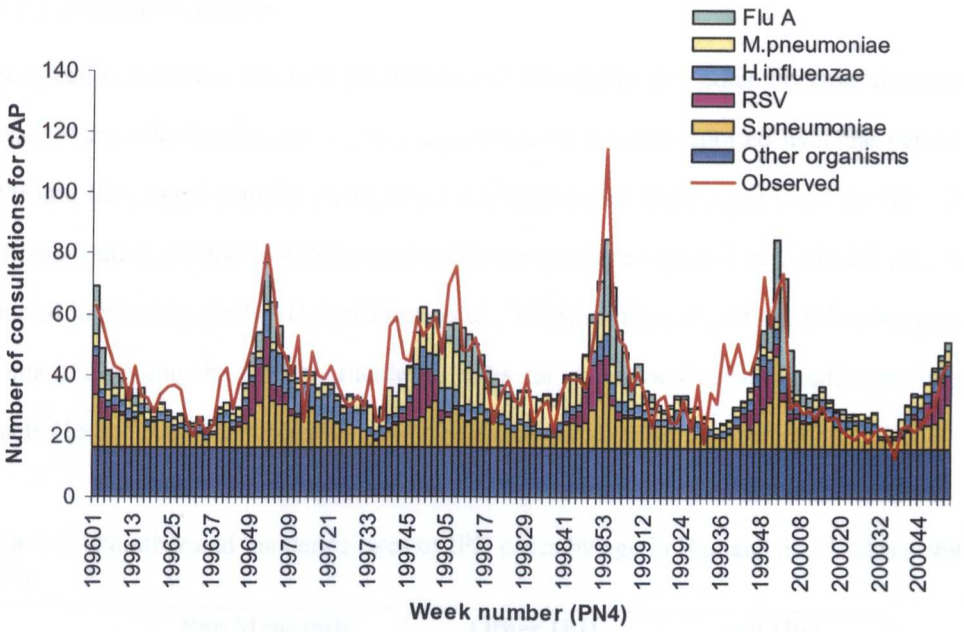
** Regression through the origin (no-intercept model)*

Table 3.4 – Estimation of the proportion of AOM attributable to specific pathogens.

Pathogen	Model AOM1* - Final model	Model AOM2	Model AOM3*
S.Pneumoniae	23%	27%	42%
Flu B	4%	4%	3%
M.Pneumoniae	12%	10%	15%
RSV	8%	7%	5%
Rhinovirus	18%	25%	35%
Adenovirus	36%	-	-
Intercept	-	27%	-
Adjusted R^2	68%	63%	58%

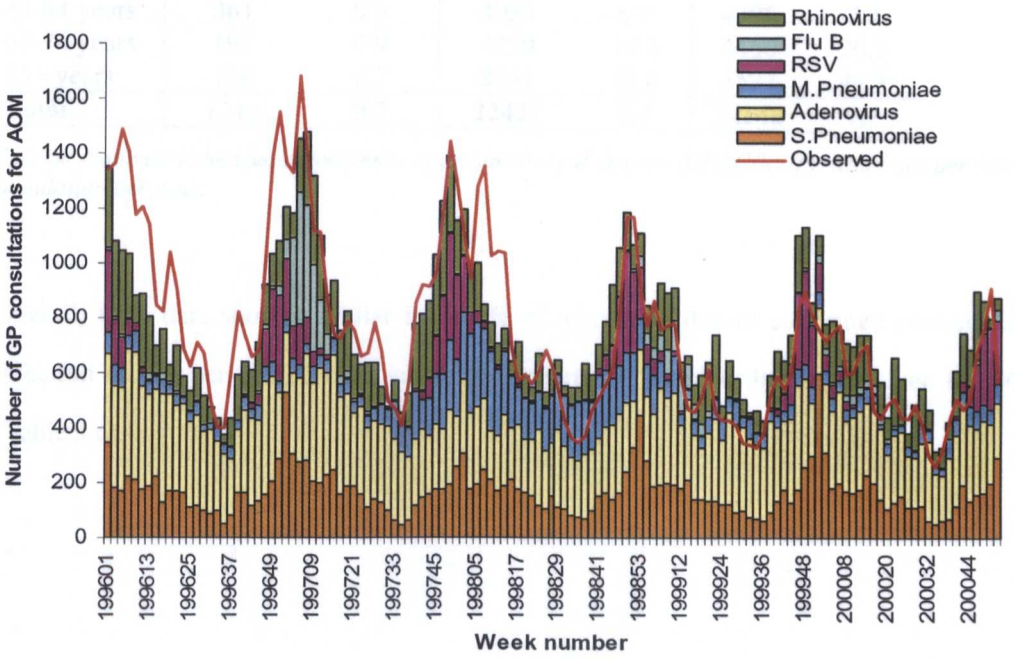
** Regression through the origin (no-intercept model);*

Figure 3.4 – Comparison of observed biweekly number of CAP episodes with estimated number derived from final best fitting model.



The best-fitting model estimated that the proportion of CAP due to S.pneumoniae is 26% (Table 3.3).

Figure 3.5 - Comparison of observed biweekly number of AOM episodes with estimated number derived from final best fitting model.



The best-fitting model estimated that the proportion of AOM due to S.pneumoniae is 23% (Table 3.4).

3.4.3 Pneumococcal disease epidemiology

3.4.3.1 Disease incidence

Age-specific incidence rates of pneumococcal meningitis and other invasive pneumococcal disease were calculated using the overall number of isolates reported over the period 1996-2000 and the annual population figures for England and Wales, produced by the Office of National Statistics (ONS). Number and incidence rates are reported in Table 3.5 and show, as reported in previous studies (Laurichesse *et al.*, 1998;Smith *et al.*, 1998), IPD rates peaking in infants and among the elderly. Incidence rates for pneumococcal meningitis are highest in infants (15 per 100,000 population) and remain low in all other age groups.

Table 3.5 - Number and incidence rates of IPD cases by age in England and Wales (1996-2000).

	Pnc Meningitis		**Other IPD**		**All IPD**	
Age group	**Cases**	**Rate**	**Cases**	**Rate**	**Cases**	**Rate**
<1 month	41	15.6	157	59.7	198	75.3
1-11 months	442	15.3	677	23.4	1119	38.6
1-4 years	221	1.7	1294	9.9	1515	11.6
5-9 years	32	0.2	316	1.8	349	2.0
10-14 years	32	0.2	138	0.8	170	1.0
15-44 years	256	0.2	3104	2.8	3360	3.1
45-64 years	361	0.6	4035	6.7	4396	7.3
65-74 years	197	0.9	4259	19.3	4456	20.2
75+ years	136	0.7	8441	43.6	8577	44.3
Total	**1719**	**0.7**	**22421**	**8.5**	**24140**	**9.2**

Source: National enhanced surveillance of pneumococcal disease (CDSC/RSIL). Rates are per 100,000 population per year.

Overall, HES data show a similar incidence of admission due to confirmed pneumococcal infection (10.84 per 100,000) as laboratory reports of invasive disease (9.2 per 100,0000) (Table 3.6).

Table 3.6 - Number and hospitalisation rates by age and clinical condition.

	Pneumococcal septicaemia [1]		*S.pneumoniae* as the cause of the disease [2]		Pneumococcal meningitis [3]		Pneumococcal pneumonia [4]		Confirmed Pneumococcal infection [1+2+3+4]		Lobar pneumonia, organism unspecified	
Age group	**Cases**	**Rate**	**Cases**	**Rate**	**Cases**	**Rate**	**Cases**	**Rate**	**Cases**	**Rate**	**Cases**	**Rate**
<1 month	14	3.96	107	30.25	29	8.20	30	8.48	180	50.89	497	140.52
1-11 months	234	8.75	824	30.81	671	25.09	485	18.14	2214	82.79	6840	255.77
1-4 years	298	2.38	498	3.97	353	2.81	900	7.18	2049	16.34	16521	131.74
5-9 years	40	0.25	121	0.74	64	0.39	372	2.29	597	3.67	6459	39.72
10-14 years	25	0.16	65	0.42	47	0.30	176	1.14	313	2.02	2665	17.20
15-44 years	381	0.37	570	0.55	367	0.35	2342	2.25	3660	3.52	19776	19.02
45-64 years	592	1.05	1050	1.86	488	0.87	2734	4.85	4864	8.62	25847	45.82
65-74 years	618	2.96	1178	5.64	256	1.23	2761	13.23	4813	23.06	30580	146.53
75+ years	1129	6.29	1527	8.51	179	1.00	5204	29.01	8039	44.81	72591	404.67
Total	**3331**	**1.35**	**5940**	**2.41**	**2454**	**1.00**	**15004**	**6.09**	**26729**	**10.84**	**181776**	**73.74**

Source: HES 1995-2000; All rates are per 100,000 population per year. ICD-10 pneumococcal codes in any of the seven diagnostic fields; from the left side of the table: A403, B953, G001, J13X.

Admissions for lobar pneumonia show a similar age distribution as laboratory-confirmed invasive infection, suggesting that these may be attributable to infection with *S.pneumoniae.*

The number and rates of otitis media hospitalisations are shown in Table 3.7 for the different age groups and also according to whether the otitis media diagnosis was reported in the first HES diagnostic field or in any of the seven available fields. A peak in the incidence rate is seen in the 1-4 years of age, although the incidence remains high in all age groups for children less than 10 years old. Almost twice as many hospitalisations are reported in children when considering any diagnostic field. This may suggest that otitis media represents a co-morbidity condition rather than the actual cause of the hospitalisation.

Table 3.7 – Otitis media number of cases and hospitalisation rates by age (1999-2000).

	Any diagnosis		**First diagnosis**	
Age group	**Cases**	**Rates**	**Cases**	**Rates**
<1 month	15	30.2	7	14.1
1-11 months	1883	345.0	1024	187.6
1-4 years	9937	406.8	4964	203.2
5-9 years	7705	236.2	4040	123.9
10-14 years	1665	52.1	1096	34.3
15-44 years	2765	13.2	1979	9.5
45-64 years	1845	16.0	1355	11.7
65-74 years	650	15.9	452	11.0
75+ years	499	13.5	278	7.5
Total	**26964**	**54.2**	**15195**	**30.5**

Rates are per 100,000 population per year. Otitis media ICD-10 codes (H65-H67) either in the first or in any diagnostic fields (HES).

3.4.3.2 Serotype distribution

The enhanced surveillance of pneumococcal disease has identified that the proportion of invasive isolates with serotype information has increased since 1996, going from 36% in 1996 to 50% in 2000 (Table 3.8). An average of 31 different serotypes were detected annually, with the 15 most prevalent types counting for 93% of the overall number.

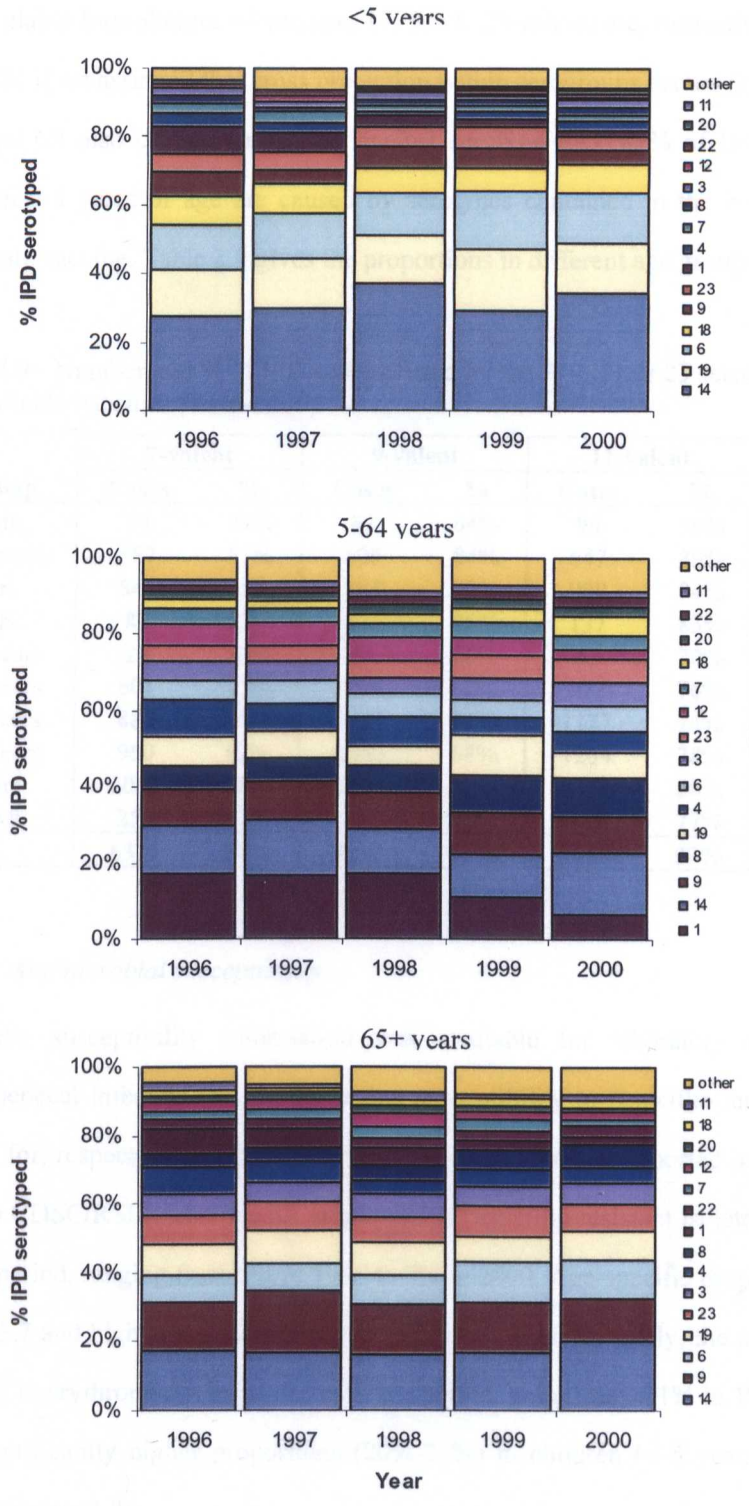
Table 3.8– Proportion of IPD isolates with serotype information (1996-2000)

	Non-typed	Typed	% Typed
1996	3071	1696	36%
1997	3238	1921	37%
1998	2843	1938	41%
1999	2776	1906	41%
2000	2393	2351	50%

Source: National enhanced surveillance of pneumococcal disease (CDSC/RSIL)

Though some changes occurred over the 5-year period in terms of the serotypes causing IPD in England and Wales, the most frequent groups remained 14, 9, 19, 6, 23 and 1 (63% of IPD). Since 1996 a significant reduction of infections caused by types 1 and 4 has been observed ($p<0.0001$) as well as an increase of types 6 ($p<0.0005$), 23 ($p=0.3019$) and 8 ($p<0.0001$). Age specific differences in the serotypes causing IPD have been observed in the past (Scott *et al.*, 1996;Hausdorff *et al.*, 2000a) and are confirmed here (Figure 3.6). Type 14 is more common in children (< 5 years) than in older age groups, though still remains the most frequent type in recent years and across all ages. Types 19 and 6 cause a higher proportion of infections in children, whereas type 1 (though it is decreasing in all age groups) is relatively more likely to be the cause of infection in 5-64 years old than in younger children or in the elderly.

Figure 3.6 – Serotype distribution of invasive isolates (1996-2000).



Source: National enhanced surveillance of pneumococcal disease (CDSC/RSIL).

The proportions of IPD in England and Wales that are caused by the serotypes contained in the available formulations of vaccines (7, 9, 11, 23-valent) are, respectively, 64%, 72%, 80% and 97% if we assumed that cross protection within serogroups occurs (i.e. vaccine containing serotype 6B also confers protection against serotype 6A). 82% of IPD cases occurring in children 0-5 years of age are caused by serotypes contained in the 7-valent pneumococcal conjugate vaccine. Table 3.9 gives the proportions in different age groups.

Table 3.9 - Number and % of IPD cases caused by the 7, 9, 11 or 23 serotypes contained in the available vaccines (1996-2000).

	7-valent		9-valent		11-valent		23-valent	
Age group	**Cases**	**%**	**Cases**	**%**	**Cases**	**%**	**Cases**	**%**
<1 month	59	47%	81	64%	96	76%	117	93%
1-11 months	587	81%	606	84%	647	89%	708	98%
1-4 years	845	88%	892	93%	908	94%	944	98%
5-9 years	88	53%	126	76%	137	83%	160	96%
10-14 years	29	43%	44	66%	47	70%	66	99%
15-44 years	601	47%	863	67%	977	76%	1249	98%
45-64 years	884	55%	1026	64%	1177	74%	1544	97%
65-74 years	960	62%	1043	68%	1204	78%	1495	97%
75+ years	2008	68%	2134	72%	2364	80%	2855	97%
Unknown	250	62%	277	69%	311	77%	386	96%
Total	**6311**	**64%**	**7092**	**72%**	**7868**	**80%**	**9524**	**97%**

3.4.3.3 Antimicrobial susceptibility

Antibiotic susceptibility information was available for laboratory reports of invasive pneumococcal infection and, in particular, susceptibility to penicillin and erythromycin was present for, respectively, 73% and 63% of the 24133 isolates reported over the period 1996-2000 to CDSC/RSIL. The overall proportion of penicillin resistant isolates increased over the 5-year period, ranging from 5% in 1996 to 7% in 2000. Age-specific proportions are shown in Figure 3.7 and highlight a similar pattern across all ages. Similarly, the proportion of isolates resistant to erythromycin increased over the period, going from 11% in 1996 to 15% in 2000, with significantly higher proportions (20%-25%) in children (< 5 years) than in older age groups (Figure 3.8).

Figure 3.7 – Proportion of invasive isolates resistant to penicillin by age group (1996-2000)

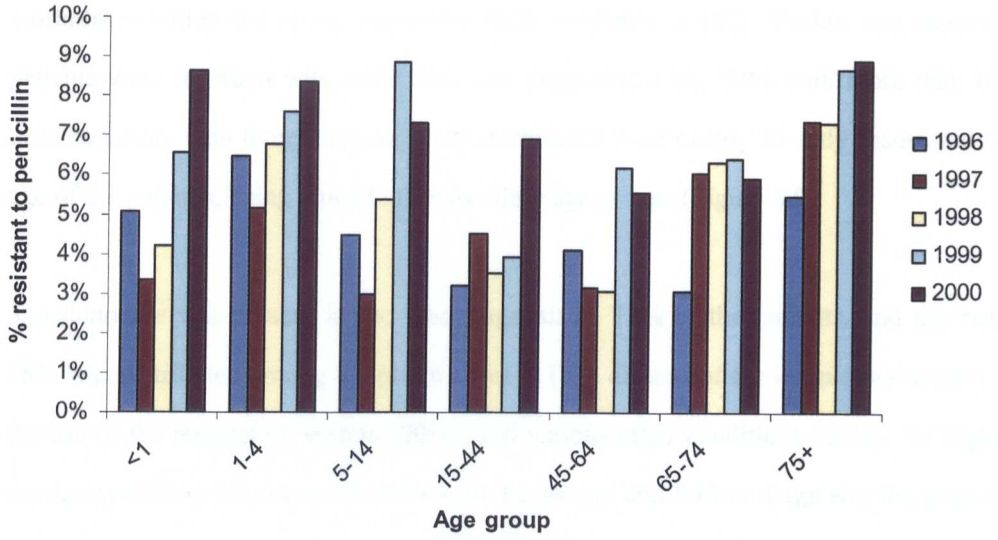
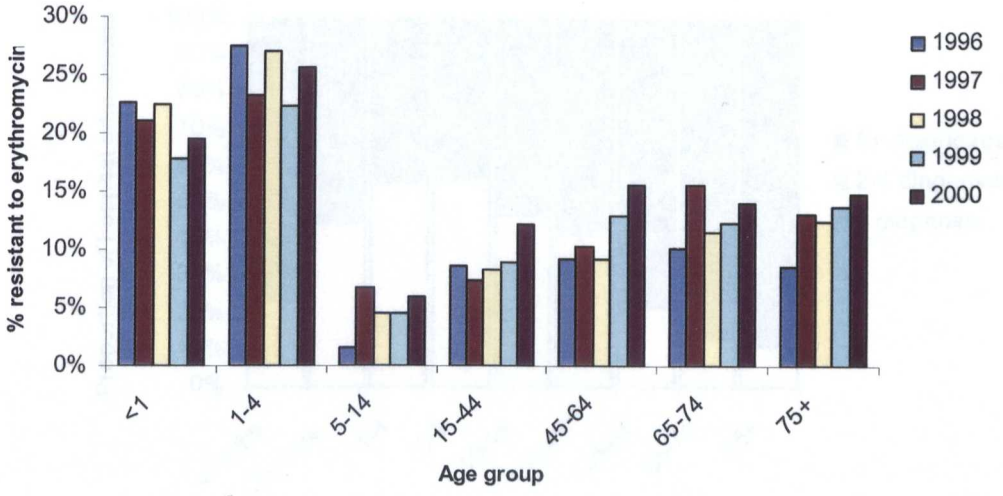


Figure 3.8 - Proportion of invasive isolates resistant to erythromycin by age group (1996-2000)



3.4.3.4 Co-morbidities of hospitalised patients

The condition of hospitalised patients was assessed, checking for the presence of co-morbidities within the seven diagnostic fields available in HES. Eighty one percent of the patients were recorded with more than one diagnostic code, 54% with more than two, and 38% had more than three diagnoses. Co-morbidities were clearly directly associated with the age of the patients, being much higher for older age groups (Figure 3.9).

S.pneumoniae was present in the first diagnosis in 72% of the patients, and the remaining 28% was distributed among neoplasm cases (11%), disease of the circulatory system (23%), disease of the respiratory system (20%), and various other conditions (46%). In Figure 3.10 the age-specific proportions are shown. In the second and further diagnoses the proportion of pneumococcus related codes were of course lower, being 15% in the second diagnosis, and 7% in the third (co-morbidities respectively: 60% and 46%, the remaining being blank fields).

Figure 3.9 – Proportion of hospitalisations reporting 1, 2-4 and 5+ diagnoses during their hospital stay (HES 1995-2000)

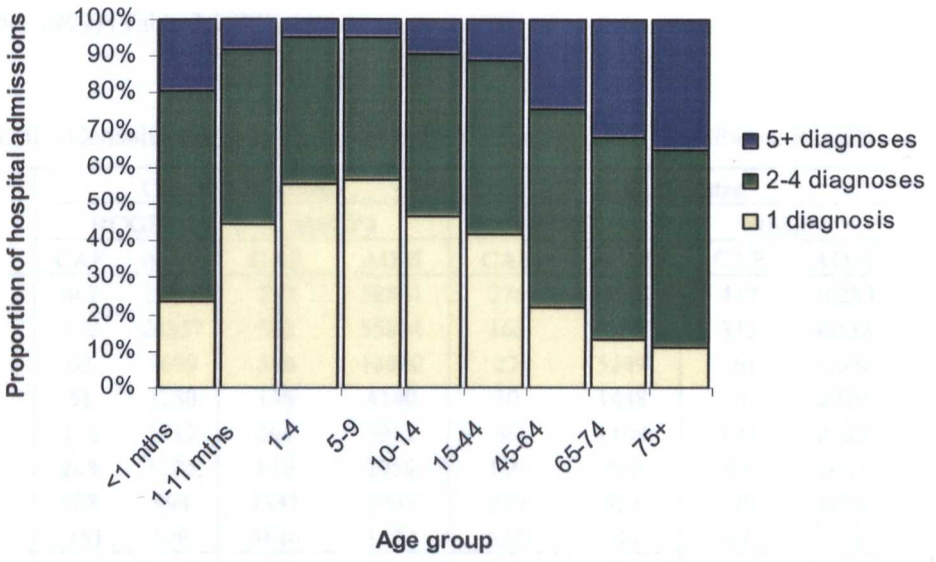
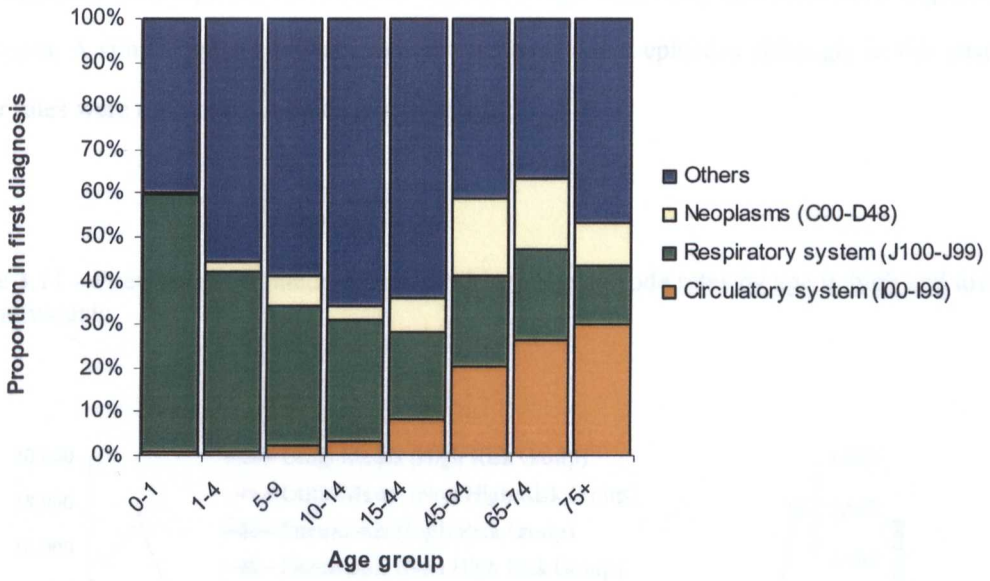


Figure 3.10 – Proportion of hospitalisations that reported a non-pneumococcal diagnosis in their first diagnostic fields by age (HES 1995-2000).



3.4.3.5 GP consultation and episode rates

Age-specific episode and consultation rates for both CAP and AOM derived from MSGP4 data (McCormick *et al.*, 1995) are higher than those routinely produced by the RCGP system (Fleming, 1999) (Table 3.10).

Table 3.10 – Consultation and episode rates for CAP and AOM (MSGP4 vs. RCGP)

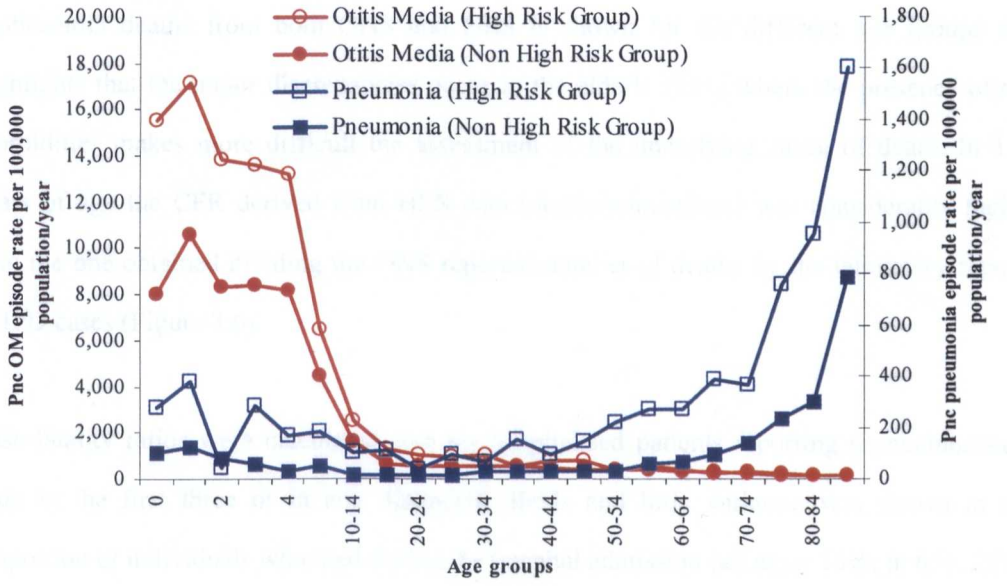
Age group	Consultation rates				Episode rates			
	RCGP		MSGP4		RCGP		MSGP4	
	CAP	AOM	CAP	AOM	CAP	AOM	CAP	AOM
<1	467	23636	717	52841	276	18332	417	36283
1-4	272	24857	582	55894	165	18121	333	40888
5-14	62	7699	310	18840	27	5249	161	13936
15-24	51	2250	146	4140	30	1448	71	2719
25-44	152	1742	301	3912	66	1169	104	2383
45-64	268	1175	610	2958	110	753	206	1663
65-74	508	994	1347	2495	229	602	539	1282
75+	1161	520	3826	1478	630	344	1681	754
Overall	**266**	**3612**	**679**	**8900**	**128**	**2507**	**282**	**6138**

Rates are per 100,000 population per year

Higher episode rates were found in patients with high-risk conditions. In Figure 3.11 pneumococcal pneumonia and AOM age-specific episode rates per 100,000 populations per

year, calculated using MSGP4 data, are reported for high and low risk individuals. For otitis media, higher rates were observed in children less than 10 years old, and almost twice as many episodes were reported for children <5 years of age when they also have other high-risk conditions. A similar pattern is observed also for pneumonia episodes although, in this case, higher rates were reported at a much later age (60+).

Figure 3.11 – Pneumococcal pneumonia and otitis media episode rates by age in high and low risk individuals.



Source: MSGP4 data. It is assumed that 26% and 23% of, respectively, CAP and AOM GP consultation are attributable to pneumococcal infection (see section 3.4.2).

3.4.3.6 Deaths

The total number of deaths for the period April 1995 to March 2000 was derived from both ONS and HES data, extracting those records for which one of the pneumococcal codes was either specified as the underlying cause of death (ONS) or recorded as the primary diagnosis of the patient (HES). Deaths reporting a pneumococcal related ICD-10 code in any of the seven diagnostic fields were also extracted from HES. The number of ONS registered deaths

from invasive pneumococcal diseases (Pnc meningitis and septicaemia) ranged between 72 and 117 per year in the period 1995 to 2000. The number of deaths from lobar (pneumococcal) pneumonia was in the range of 1807 to 2064 (Table 3.11). These figures represent around 70% of the total number of deaths reported in HES for patients admitted with a pneumococcal meningitis or septicaemia code in the first diagnostic field though only around 40% of cases that died in the hospital and for which the pneumococcal related diagnosis was extracted from any of the seven diagnostic fields. The apparent under-reporting of deaths in ONS may represent cases that die with a pneumococcal related condition but for which the underlying cause of death (as reported in the death certificate) was non-pneumococcal specific. In Figure 3.12 the number of reported pneumococcal meningitis and septicaemia deaths from both ONS and HES is shown for the different age groups and highlights that the major discrepancies occur in the elderly (75+) where the presence of co-morbidities makes more difficult the assessment of the underlying cause of death. In 15+ years of age the CFR derived from HES data (deaths/admissions) was considerably higher than the one obtained dividing the ONS reported number of deaths by the laboratory reports of IPD cases (Figure 3.6).

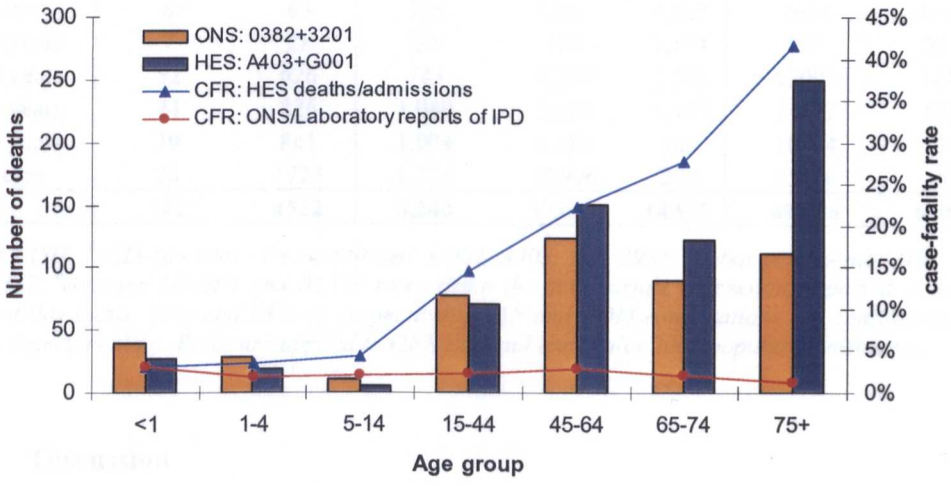
Case-fatality ratios were calculated also for hospitalised patients reporting a pneumococcal code in the first three or in any diagnostic fields and little variation was shown in the proportion of individuals who died during the hospital admission (all ages: 13%; in 65+: 21%-28%).

Table 3.11 – Number of deaths from pneumococcal disease

Year	ONS[a]		HES - first diagnosis[b]		HES - any diagnosis[b]	
	Lobar (pnc) pneumonia	IPD	Lobar (pnc) pneumonia	IPD	Lobar (pnc) pneumonia	IPD
95/96	1907	94	2468	133	4553	219
96/97	2064	117	2841	140	5286	268
97/98	1807	99	2738	132	5323	223
98/99	1991	104	3471	114	6357	229
99/00	2059	72	3696	127	6853	234

[a]*The ICD-9 coding system was used for ONS records until 2000 data (lobar, pneumococcal pneumonia code = 481, IPD = 0382 (pnc septicaemia) + 3201 (pnc meningitis);* [b] *The ICD-10 coding system was used in HES since 1995 (lobar, pneumococcal pneumonia code = J181 (lobar pneumonia organism* unspecified) + J13 (pneumococcal pneumonia), IPD = A403 (pnc septicaemia) + G001 (pnc meningitis).

Figure 3.12 – Number of Pnc meningitis and septicaemia deaths reported to ONS and to HES and CFR by age.



Deaths reporting the following ICD-9(10) codes as the underlying cause of death (ONS) and the as the primary diagnosis (HES): pneumococcal meningitis: 3201(G001); pneumococcal septicaemia: 0382(A403).

3.4.3.7 Burden of disease

The burden of pneumococcal disease was derived from incidence, hospitalisation and consultation rates provided in this chapter and is summarised in Table 3.12. The proportion of consultations to the general practitioner for CAP and AOM attributable to the pneumococcus were estimated using the results of the multivariate regression analysis (3.4.2) where we found that 26% of CAP and 23% of AOM GP consultations may be attributable to

S.pneumoniae infection. Otitis media represents a major component of the overall burden of disease with over 650,000 consultations to the general practitioner per year. Of these, around 60% occurs in children less than 10 years of age. Similarly 70% of OM hospitalisation occurs in children as well as around 40% of pneumococcal meningitis cases. The burden of pneumococcal disease in the elderly is represented mostly by episodes of pneumococcal pneumonia and septicaemia. Fifty-three and 60% of hospitalisations for, respectively, Pnc confirmed disease and lobar pneumonia occurs in 65+ year of age.

Table 3.12 – Burden of pneumococcal disease in England and Wales.

	Laboratory reports[a]		Hospitalisations[b]			GP consultations[c]	
Age group	Pnc meningitis	Other IPD	Pnc confirmed	Lobar pneumonia	OM	Pnc pneumonia	Pnc OM
<1 year	93	161	488	1,500	1,055	937	53588
1-4 years	43	253	418	3,371	5,200	2839	237629
5-9 years	6	63	125	1,355	4,227	1654	104156
10-14 years	7	28	69	589	1,174	875	25160
15-44 years	52	626	783	4,228	2,102	13093	144547
45-64 years	74	826	1,069	5,680	1,455	14157	58930
65-74 years	39	841	1,004	6,382	480	10504	17476
75+ years	28	1723	1,771	15,996	298	25626	9082
Total	**342**	**4522**	**5,240**	**37,602**	**14,937**	**69,686**	**650,568**

[a]CDSC/RSIL; [b]ICD-10 codes - Pnc confirmed: G001, A403, J13, B953; Lobar pneumonia: J181; OM: H65-H67; [c]Average MSGP4 and RCGP rates (from the multivariate regression, reported in section 3.4.2 of this thesis, 26% and 23% of, respectively, CAP and AOM consultations are considered to be due to S.pneumoniae). Rates are applied to ONS England and Wales 2000 population estimates.

3.5 Discussion

The aims of this chapter were to explore and compare the available data sources for pneumococcal disease, to describe the epidemiology of *S.pneumoniae* infection and to investigate whether any change occurred in the last few years in the incidence of invasive and non-invasive disease. From the public health perspective, this information is necessary in order to monitor the short and long term impacts of pneumococcal vaccination strategies (discussed in section 2.4) and to provide economic evaluations analyses for the proposed vaccination schedules.

A number of surveillance systems are in place for England and Wales and contribute to the understanding of the burden of pneumococcal disease. However, whereas IPD cases are

generally diagnosed through laboratory-based methods, the aetiological responsibility of less severe pneumococcal-related clinical conditions, such as CAP and OM, is generally left unspecified. This generates a gap in the knowledge about the real burden of pneumococcal disease and, in particular, on its contribution to all those clinical diagnoses that may or may not be due to pneumococcal infection. A number of studies have attempted to estimate the real burden of pneumococcal disease, either increasing the number of reported cases applying the sensitivity of alternative laboratory diagnostic methods (i.e. PCR, latex agglutination) to unspecified clinical conditions (McIntosh & Booy, 2002), or reviewing hospital admissions to estimate the proportion likely to be attributable to *S.pneumoniae* infection (Djuretic *et al.*, 1998). Moreover, capture-recapture analysis has been utilised to improve estimates of disease incidence and deaths from pneumococcal meningitis among adults in England (Gjini *et al.*, 2004). The authors estimated a sensitivity of 40% (95% CI 37% to 44%) of the CDSC/RSIL enhanced surveillance system and 46% for HES (95% CI 42% to 50%). These estimates will be used in Chapter 9, where the cost-effectiveness of the conjugate vaccination programme will be evaluated taking into account possible underestimates of the burden of disease from the national surveillance systems.

In this chapter, we tried to quantify the amount of pneumococcal disease, invasive and non-invasive, that is present in England and Wales, using both national surveillance databases and multivariate regression techniques (thanks to the clear seasonality of pneumococci) to estimate the proportion of GP consultations for both pneumonia and OM that is attributable to *S.pneumoniae* infection. The strength of this modelling technique has been shown in the past when similar questions were addressed for rotavirus (Ryan *et al.*, 1996) and hospital admissions for RSV (Muller-Pebody *et al.*, 2002).

As shown in previous studies (Smith *et al.*, 1998;Miller *et al.*, 2000;Sleeman *et al.*, 2001;Kyaw *et al.*, 2002) the estimated burden of pneumococcal disease in England and Wales is considerable, with incidence rates of both IPD and non-IPD peaking in children (<5 years) and in the elderly (75+ years). Morbidity appears to be related to the presence of high-risk conditions, with over 80% of hospitalised patients presenting with more than one diagnosis.

In particular, neoplasm and diseases of the respiratory and circulatory systems are common co-morbidity conditions.

The potential threat of serotype replacement occurring as a consequence of vaccination requires the monitoring of the changes in the serotype distribution of pneumococcal disease patients and, ideally, asymptomatic carriers. Though some changes were observed in the serotypes causing IPD in England and Wales over the 5-year period 1996-2000, no new serotypes emerged. However, a significant reduction was observed for some of the types (i.e. 1, 4) as well as a significant increase for others (i.e. 6, 23, 8). Moreover, age specific differences in the prevalence of pneumococcal types have been shown with some types causing IPD more frequently in children than in adults (i.e. 14, 19, 6).

IPD patients were found to be less susceptible to antibiotic (penicillin and erythromycin) in more recent years than in 1996. Penicillin non-susceptibility levels increased similarly over the 5-year period in all age groups. Children less than five years of age were found to be erythromycin resistant in much higher percentages compared to older age groups.

Morbidity and mortality data presented in this Chapter will be used in Chapters 5 and 9 of this work, where economic evaluations will be performed. Moreover, in Chapter 6, the dynamics of pneumococcal carriage and transmission will be investigated and comparisons will be produced between serotypes asymptomatically carried and those causing severe disease.

CHAPTER 4 - THE EFFECTIVENESS OF THE 23-VALENT PNEUMOCOCCAL POLYSACCHARIDE VACCINE

4.1 Aims

- To determine the level of protection that the pneumococcal polysaccharide vaccine (PPV) confers to high and low risk elderly in order to then inform the cost-effectiveness analysis of Chapter 5. This will be achieved by the following:

    - Systematic literature review of published randomised and quasi-randomised controlled trials (RCT and QRCT) looking at vaccine efficacy (VE) of PPV;
    - Meta-analysis to estimate overall pooled efficacy level among individuals at high and low-risk of pneumococcal infection;

- To compare the pooled estimates to results of other published meta-analyses and case-control studies (CCS).

4.2 Introduction

The current and the following chapter are intended to investigate, respectively, the effectiveness of the currently available 23-valent PPV, and to determine the economic acceptability of alternative vaccination programmes with PPV in England and Wales. The work presented in these two chapters was used to inform the UK Joint Committee on

Vaccination and Immunisation (JCVI) (which advices the Departments of Health on National Vaccine Policy) on the effectiveness and cost-effectiveness of the current (at the time, May 2002) and alternative programmes. The content of these two chapters has been published (Melegaro & Edmunds, 2004a;Melegaro & Edmunds, 2004b).

At the time of the analysis the 23-valent PPV was recommended only to individuals older than 2 years of age with a high risk of pneumococcal infection (section 2.4.1) (Salisbury & Begg, 1996). However, discussions were ongoing on the degree of protection afforded by PPV in these categories and, in addition, questions on whether it would have been appropriate to extend the vaccination programme to the healthy elderly (i.e. without high-risk conditions) were also under consideration by the JCVI. This subgroup of the population has always experienced high incidence rate of pneumococcal disease (Laurichesse *et al.*, 1998;Smith *et al.*, 1998;Sleeman *et al.*, 2001;Kyaw *et al.*, 2002) and had recently been recommended to receive the influenza vaccine (www.dh.gov.uk, last accessed September 2004). This provided an opportunity for the introduction of the 23-valent-pneumococcal vaccines for all the elderly since both vaccines may be given at the same time (Fedson, 1998;Ament *et al.*, 2000).

However, the level of protection afforded by PPV in the general elderly population and among specific at-risk categories has been highly debated (Jefferson & Demicheli, 2002;French, 2003). Several randomised (or quasi-randomised) clinical trials, case-control and indirect cohort studies investigated the vaccine efficacy (VE) against pneumococcal pneumonia and/or IPD, but none of the clinical trials had sufficient power to detect a significant effect of the vaccine. Meta-analyses were thus applied to obtain an overall pooled estimate of VE but none of these focused exclusively on elderly patients and, in particular, none differentiated between the general elderly and elderly at a higher risk of infection. The level of protection of the vaccine in these groups represented a crucial aspect in the debate on whether or not to extend the vaccination programme to all the elderly.

4.3 Methods

4.3.1 Inclusion criteria

A PubMed literature search (without any year or language restriction) was used to identify published studies on PPV efficacy. The following keywords were used to identify relevant articles: "pneumococc*", "vaccination", "pneumococcal vaccine", "immunisation" and "clinical trial". Papers that included words such as "children", "infants", "conjugate", "carriage" and "otitis media" in the title, were excluded from the list of selected papers. Previous meta-analysis and reviews were also extracted and checks were made in order to have a complete list of studies. References of the retrieved papers were also examined. The inclusion criteria that were adopted to select the papers to be part of the analysis were:

1. All randomised and quasi-randomised controlled trials with a well-defined randomisation or quasi-randomisation process and with a PPV and a control group (placebo or a control vaccine). A trial is defined *quasi-randomised* when the method of allocating participants to different forms of care is not truly random (i.e. allocation by date of birth, day of the week, medical record number, month of the year, or the order in which participants are included in the study);
2. Studies which targeted immunocompetent and immunocompromised individuals (50+ years of age);
3. Studies that assessed at least one of the following endpoints: pneumococcal pneumonia and/or invasive pneumococcal disease.

The definition of pneumococcal pneumonia that was used consisted of a clinically and radiographically confirmed diagnosis of pneumonia, with *S.pneumoniae* cultured from sputum or a nasal swab. Diagnoses made on the basis of a twofold rise in pneumolysin antibody level in paired serum samples were also accepted, due to the high sensitivity (97.8%) and specificity (83.4%) that was shown by Leinonen and colleagues (1990) for these tests, using standard procedures (i.e. blood or culture of sputum) as reference methods (see section

2.2.4 for discussion on sensitivity of different laboratory tests). Similarly, the technique of pneumococcal antigen detection by electrophoresis of urine specimen was also accepted as a diagnostic method. Invasive pneumococcal disease patients were defined as bacteraemic cases with *S.pneumoniae* isolated from blood or any other usually sterile body fluid (e.g. peritoneal, pleural, cerebrospinal, or joint). Although the two endpoints were not consistently assessed throughout the studies (with some studies that included bacteraemic cases within the pneumococcal pneumonia group and some others that considered the two groups distinctively) the following analysis considers them separately. However, estimates of vaccine efficacy for pneumococcal disease (invasive and non invasive) are given in the sensitivity analysis where the number of cases of pneumococcal pneumonia and IPD are summed up for each trial and a unique level of protection is produced.

4.3.2 Information collected from the eligible trials

WJ Edmunds (HPA, CDSC, Modelling and Economics Unit) and myself independently read the selected papers and extracted information on study design (type of interventions, number of serotypes included in the vaccine (valency), follow-up time) and on the participants (demographic characteristics and background health conditions) of each trial. Similarly, the number of pneumococcal pneumonia and bacteraemic cases was assessed for each study and compared to that published in previous meta-analyses.

The Jadad's system (Jadad, 1996) was used to score each report according to whether or not randomisation, blinding and description of withdrawals were part of the study. One point was given for each of these, and one additional point was added or subtracted when either methods of randomisation or blinding were, respectively, well described by the authors or inadequately performed. The maximum possible score was five. When discrepancies in the quality evaluation existed, we met and discussed to resolve them. All the studies that were not reporting clear information about the age of the participants, about the randomisation process or the diagnostic procedures that were used were excluded from the analysis.

Information about the health conditions of all the study populations was collected and the proportion of high-risk individuals in each trial was assessed (where high-risk was defined as those categories to which the vaccine was recommended in the UK (Salisbury & Begg, 1996)). As most of the studies included in their analysis at least a proportion of institutionalised patients or elderly with some chronic condition, we decided to consider as 'high-risk' those study populations that had at least 50% of the individuals with some chronic condition or immunodeficiency. When the proportion was below this threshold, then the trial was considered to be a study of the general elderly population. This criterion was widened in the sensitivity analysis so that all the trials in which more than 20% of the study population were at high-risk were included when calculating vaccine efficacy in high-risk groups.

4.3.3 Statistical Methods

Several statistical techniques are available to estimate summaries of the effect size (i.e. OR) in different trials. One of the most crucial differences among them is whether or not they incorporate between-study variation (heterogeneity) and, consequently, whether the model used is a fixed or a random effect model. This latter type of model, which is appropriate when significant heterogeneity is present between studies, produces a more conservative estimate (i.e. wider confidence intervals) of the pooled effect size.

Here we assumed that the trials considered were a random sample from a hypothetical population of studies, and thus the DerSimonian & Laird (DerSimonian & Laird, 1986) random effect model Odds Ratio (OR) was adopted in the base-case. This computes a weighted average of individual studies' OR, taking into account both sampling variation and between study heterogeneity.

All analyses were performed using *Stata 6.0* and the results are presented using funnel plots with single and overall OR and related 95%CIs. The results obtained were compared with previous meta-analyses. The definition of vaccine efficacy used was VE=(1-OR)*100(%) (Orenstein *et al.*, 1988;Giesecke, 1994), with confidence intervals of the pooled estimate

obtained, similarly, as a function of those derived for overall OR. Odds ratios are good approximation of relative risks when outcomes are comparatively rare, as in the studies included in this analysis, and have desirable properties when combining results across studies (Oxman *et al.*, 1994). Conventional levels of statistical significance (i.e. 5%) were used throughout the analysis.

4.3.4 Sensitivity analysis

Sensitivity analyses were performed to assess whether different model assumptions would have changed the results. The Mantel-Haenszel fixed effect method was adopted under the assumption that the differences among the results of the studies were due to chance alone. Further sensitivity tests were performed by modifying the inclusion criteria in the analysis and considering only randomised controlled trials.

Moreover, case-control and indirect cohort studies were also included in the sensitivity analysis to assess whether their results are consistent with findings from randomised controlled trials. We evaluated the effects their inclusion had on the overall pooled estimates for VE against IPD in high and low risk elderly, and compared this to the results produced using randomised and quasi-randomised trials.

4.4 Results

4.4.1 Literature review

Of all the studies retrieved from the literature search, six randomised and three quasi-randomised clinical trials were selected that satisfied the inclusion criteria (Table 4.1), although three of them (Kaufman, 1947;Gaillat *et al.*, 1985;Honkanen *et al.*, 1999) were methodologically weak according to the Jadad scores assigned by the two reviewers. Of the nine studies, five were European studies (Gaillat *et al.*, 1985;Klastersky *et al.*, 1986;Koivula *et al.*, 1997;Ortqvist *et al.*, 1998;Honkanen *et al.*, 1999), three American (Kaufman,

1947;Simberkoff *et al.*, 1986;Davis *et al.*, 1987), and one Canadian (Leech *et al.*, 1987). The study by Kaufman and colleagues (1947), although it is one of the largest trials, and has the largest mean effect (both for pneumonia and IPD) (Table 4.1), was not included in our base case pooled estimates due to the methodological weaknesses that were present in the design and implementation of the study. It was an open trial, performed over a period of six years during which the participants were recruited using different randomisation procedures. Indeed, the first cohort recruited into the trial was not randomised and patients volunteered for the injection. Furthermore, it used 2 and 3-valent vaccines, and 21% of the participants were under 60 years of age. Three studies that were included in previous meta-analyses were excluded from ours due to the presence of healthy young adults in their study population (Austrian *et al.*, 1976;Smit *et al.*, 1977;Riley *et al.*, 1977) (Table 4.2). The mean age of the study population was available for all the trials used in our analysis (range: 61-74 yrs.), as well as the proportion of chronically ill elderly (range: 27%-100%). Four studies that were undertaken among elderly with respectively, chronic obstructive pulmonary disease (COPD), bronchogenic carcinoma, or various chronic conditions, as defined in the recommendations, were defined as studies of high-risk groups (HRG) (Klastersky *et al.*, 1986;Simberkoff *et al.*, 1986;Davis *et al.*, 1987;Leech *et al.*, 1987). In addition, a Swedish study (Ortqvist *et al.*, 1998) was included in the HRG on the basis of the history of community-acquired pneumonia that the study participants had experienced, and due to the high proportion of HR individuals (58%) that were present in the trial. Three studies were undertaken among elderly patients not experiencing, in high percentages, specific chronic conditions (Gaillat *et al.*, 1985;Koivula *et al.*, 1997;Honkanen *et al.*, 1999). Their study participants were considered representative of the general elderly population, although they all reported a proportion of high-risk individuals in the range of 27-34% (Table 4.1). In the sensitivity analysis the high-risk threshold was reduced to 20% and these studies were included in the HRG.

In accordance with previous meta-analyses (Hutchinson *et al.*, 1999;Moore *et al.*, 2000;Cornu *et al.*, 2001), the study by Davis and colleagues (1987) was excluded from the analysis for our base case estimate of VE against IPD. Although, in fact, a case of pneumococcal bacteraemia was reported among the participants, this occurred during a terminal episode of pneumonia in

a severely ill patient who had been hospitalised on a long-term basis for respiratory insufficiency, repeated urinary tract infections, cardiac failure and acute pancreatitis. The effect of this case on the estimate of VE against IPD in HRG was explored in the sensitivity analysis.

4.4.2 Statistical analysis

The individual trials and summarised OR [95% CI] are shown in Figures 4.1-4.2, for the two study outcomes, according to the different level of risk of the study participants. The overall results obtained when RCT and case-control studies were considered together are presented in the sensitivity analysis and shown in Figure 4.3.

4.4.2.1 Vaccine efficacy against pneumococcal pneumonia

A low level of protection of the polysaccharide vaccine against pneumococcal pneumonia among elderly individuals has already been shown (Simberkoff *et al.*, 1986;Koivula *et al.*, 1997;Ortqvist *et al.*, 1998;Honkanen *et al.*, 1999). Among the randomised controlled trials included in the analysis, seven studies had pneumococcal pneumonia diagnosed with one of the methods outlined in the inclusion criteria. All of them showed a negative or non-significant effect against pneumococcal pneumonia in the elderly, with VE ranging from -28% [-153% to 35%] (Simberkoff *et al.*, 1986) to 76% [-150% to 98%] (Klastersky *et al.*, 1986).

Table 4.1 - Randomised and quasi-randomised trials on VE against pneumococcal pneumonia and IPD

Reference	Jadad Score	Study type	Type of randomisation	Study Population	Mean age in years	Sample size – vacc.	Sample size - controls	PP in vaccinated (control) #	IPD in vaccinated (control) #	HRG (%)	Vaccine type	VE for PP (95% CI)	VE for IPD (95% CIs/p-value)
Kaufman *et al.*(1947) [US]	0	QRCT - Open	Not randomised in the first 2 yrs. Randomisation unclear in the last 4 yrs.	Institutionalised elderly in New York City Home & Hospital	68.7 (79% is 60+)	5750	5153	34 (96) [H+, F-, M-, C-]	8 (34) [H+, F-, C-, M-]	No (n.a.)	2 and 3-val	69% (53% to 80%)	79% (54% to 92%)
Gaillat *et al.*(1985) [FRANCE]	0	QRCT - Open	Randomisation done after stratifying by the level of risk.	Elderly hospitalised/nursing home patients	74 (all 55+)	937	749	3 (9) [M+, H-, C-, F-]	0 (1) [F+, H+, C+, M-]	Mix (27%)	14-val	74% (2% to 93%)	100% (n.s.)
Klastersky *et al.*(1986) [BELGIUM]	3	RCT -Single blind (recipients unaware)	Vaccine in numbered boxes, prepared according to prior randomisation by vaccine manufacturer.	High risk adults and elderly with bronchogenic carcinoma	61 (all 42-78)	26	21	1 (3) [C+, M-, F+, H-]	1 (1) [F+, H+, M+, C+]	Yes (100%)	17-val	76% (-150% to 98%)	20% (n.s.)
Davis *et al.*(1987) [US]	3	RCT -Double blind	Randomisation based on a table of random numbers.	High risk elderly with COPD	63 (all 50+)	50	53	1 (0) [M-, H+, F+, C-]	n.a. [F-, C+, H+, M+]	Yes (100%)	14-val	Infinite	n.a.
Leech *et al.*(1987) [CANADA]	3	RCT -Double blind	Randomisation done after stratifying by age and FEV_1**.	High risk elderly with COPD	67 (all 40-89)	92	97	n.a.	1 (0) [F+, M+, H+, C-]	Yes (100%)	14-val	n.a.	Infinite
Simberkoff *et al.*(1986) [US}	3	RCT - Double blind	Randomisation done using sequence of numbers to patients and syringes.	High risk elderly/ambulatory veteran	61.3 (82% is 55+)	1145	1150	19 (15) [H-, M+, C+, F+]	2 (1) [F+, H+, M-, C-]	Yes (100%)	14-val	-28% (-153% to 35%)	-101% (n.s.)
Koivula *et al.* (1997) [FINLAND]	3	RCT - Single blind (recipients unaware)	Randomised done by computer.	All the elderly inhabitants of Varkaus	69* (all 60+)	1364	1473	26 (33) [C-, M+, H-, F-]	n.a. [F+, C+, M+, H+]	Mix (34%)	14-val	15% (-43% to 50%); HRG: 56% (3% to 80%)	n.a.
Ortqvist *et al.*(1998) [FINLAND]	5	RCT – Double blind	Random numbers given by vaccine manufacturer.	Middle-aged and elderly treated in hospital for CAP	69.3 (all 50-85)	339	352	19 (16) [F-, H-, M+, C+]	1 (5) [F-, C+, M+, H-]	Yes (58%)	23-val	-25% (-147%-37%)	79% (-77% to 98%)
Honkanen *et al.*(1999) [FINLAND]	0	QRCT – Open	Randomisation by year of birth: odd/even.	Elderly living in 35 adm. districts	73.6 (all 65+)	13980	12945	52 (40) [C-, M-, H-, F-]	2 (5) [M-, C-, H-]	Mix (31%)	23-val	-20% (-90% to 20%)	60% (-40% to 90%)

*PP=pneumococcal pneumonia; QRCT=quasi-randomised controlled trial; RCT=randomised controlled trial; COPD=chronic obstructive pulmonary disease; CAP=community-acquired pneumonia; n.a.=not available; *=median age; ** FEV1 = forced expiratory volume in 1 second; # [H+(-)] = in agreement (in disagreement/not included) with Hutchinson's meta-analysis (F=Fine, M=Moore, C=Cornu).*

Overall pooled estimates of the odds ratio were produced in order to assess the significance of previous findings and, most importantly, to determine the level of protection by risk group. A non-significant and very low level of protection of the vaccine was found; VE 16% [-50% to 53%] using a random effects model including the three trials (Gaillat *et al.*, 1985;Koivula *et al.*, 1997;Honkanen *et al.*, 1999) representative of the general elderly population (Figure 4.1a). Bacteraemic cases were excluded from the calculation. The estimated mean protective effect of vaccination was actually negative (though not significant) when considering the studies that were performed among high-risk elderly (Klastersky *et al.*, 1986;Simberkoff *et al.*, 1986;Davis *et al.*, 1987;Ortqvist *et al.*, 1998), VE=-20% [-92% to 25%] (Figure 4.1b).

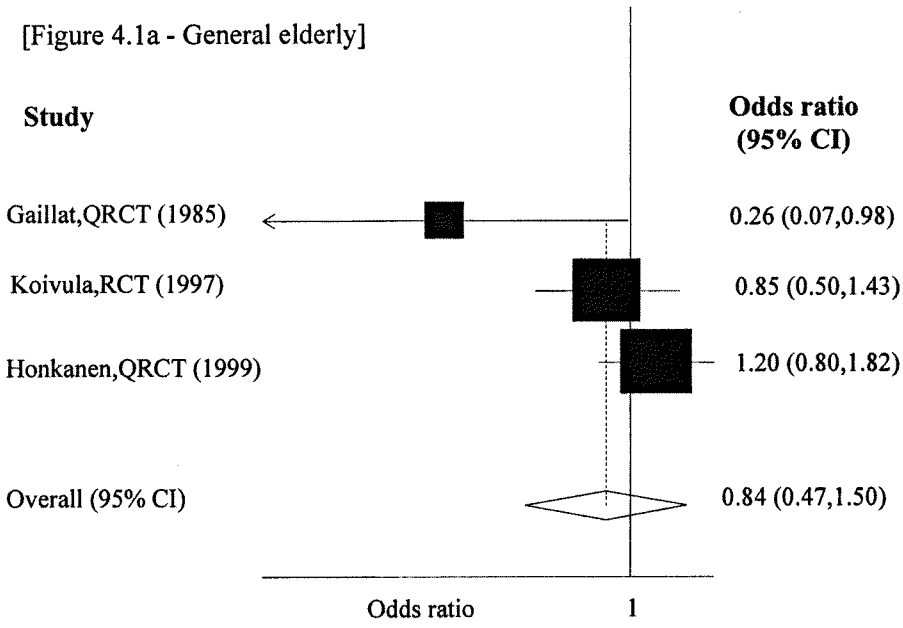
Comparing to previous meta-analyses (Table 4.2), a level of protection of 60% [44% to 71%] and 2% [-89% to 49%] in, respectively, low and high risk adults was shown by Fine and colleagues (1994). Their estimates of VE, which are higher than those reported here, were influenced by the inclusion of trials that were performed among healthy young adults (Austrian *et al.*, 1976;Smit *et al.*, 1977;Riley *et al.*, 1977). Similarly, another two meta-analyses (Hutchinson *et al.*, 1999;Cornu *et al.*, 2001) found a positive level of protection against pneumonia, but these estimates might still be a consequence of the inclusion of studies performed in healthier individuals. For HRG, Cornu and colleagues (2001) found a negative and non-significant vaccine protection, in accordance with this analysis. Moore and colleagues (2000) found a higher estimate of VE although the populations they allowed for in their analysis were, exclusively, young healthy adults.

4.4.2.2 Vaccine efficacy against invasive pneumococcal disease

The level of protection against invasive pneumococcal disease was assessed in six out of the eight studies that were considered in the analysis. Two trials studied the protective effect of the vaccine against IPD in the general elderly population (Gaillat *et al.*, 1985;Honkanen *et al.*, 1999). Both of them suggested that the vaccine was protective, though none of them obtained a statistically significant result (Figure 4.2a). The pooled estimate showed an unsignificant reduction in the incidence of pneumococcal bacteraemia, VE=65% [-49% to 92%].

Four trials were performed among the elderly at a higher risk (Klastersky *et al.*, 1986;Simberkoff *et al.*, 1986;Leech *et al.*, 1987;Ortqvist *et al.*, 1998). The results of these were scattered around a zero effect and all had a lack of statistical power. The pooled estimate of efficacy was weakly positive, VE=20% [-187% to 78%] (Figure 4.2b). A further two trials (both quasi-randomised) were performed on elderly populations which had between 20% and 50% of high-risk individuals (Gaillat *et al.*, 1985;Honkanen *et al.*, 1999). The inclusion of these two trials improved our mean estimate of vaccine efficacy in the high-risk elderly, though this remained non-significant, VE=44% [-45% to 79%].

Figure 4.1– Published odds ratios and associated 95%CI for pneumococcal pneumonia.



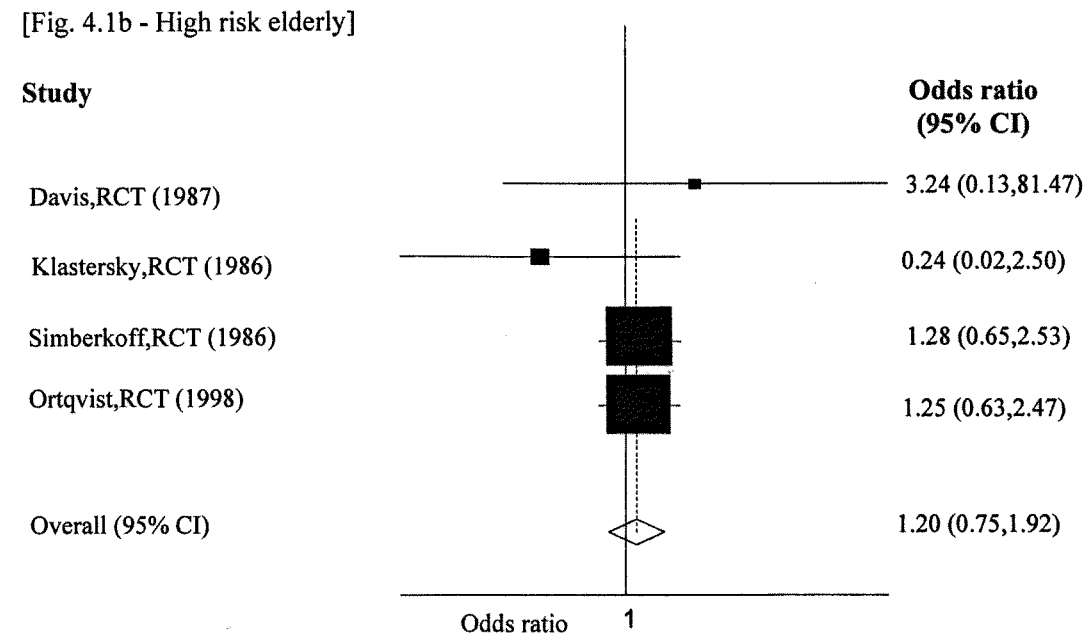
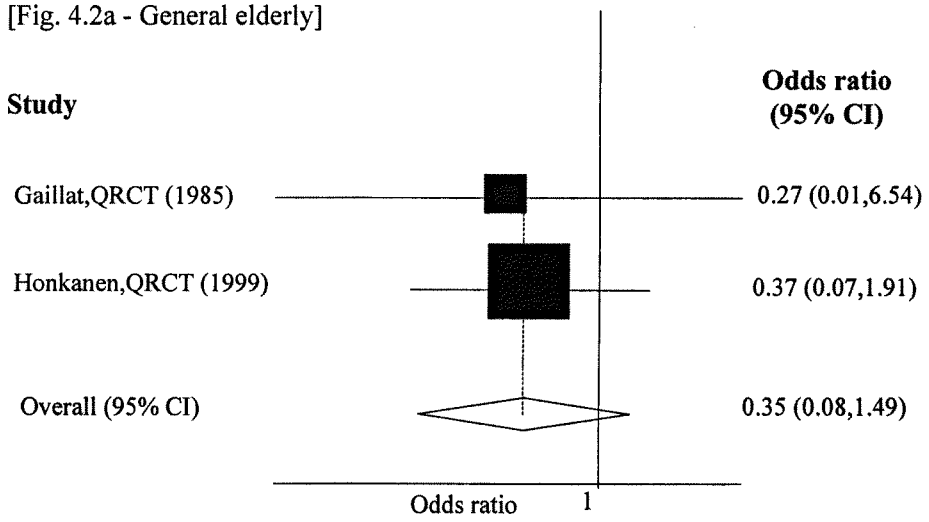


Figure 4.2– Published odds ratios and associated 95%CI for invasive pneumococcal disease.

[Fig. 4.2a - General elderly]



[Figure 4.2b – High-risk elderly]

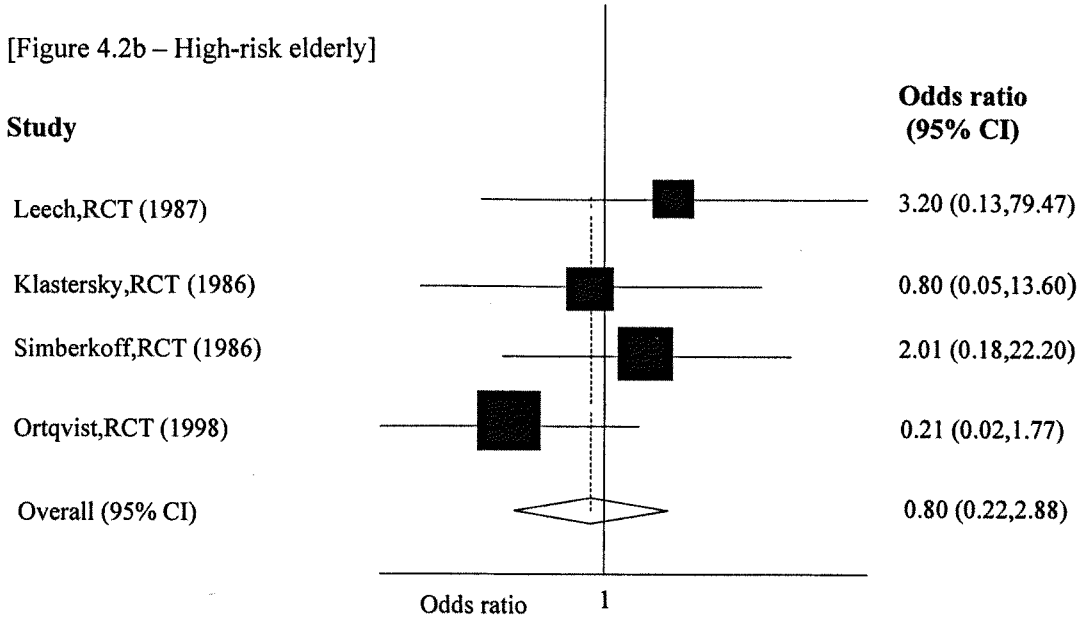


Table 4.2 - Meta-analyses and studies included in the calculation of the overall odds ratio for IPD and pneumococcal pneumonia

	Fine 1994			Hutchison 1999	Moore 2000		Cornu 2001		Melegaro 2004		
	All studies	**LRG**	**HRG**	**All studies**	**Healthy**	**HRG**	**All studies**	**HRG**	**LRG**	**HRG[a]**	**MIX[b]**
VE against IPD	66% (52%- 76%)	68% (54%-78%)	-23% (-449%-72%)	73% (50%-85%)	82% (66%-91%)	47% (-94%-86%)	71% (58%-80)	42% (0%-82%)	65% (-49%-92%)	20% (-188%-78%)	44% (-45%-79%)
VE against pneumococcal pneumonia	53% (37%-65%)	60% (44%-71%)	2% (-89%-49%)	42% (28%-53%)	84% (77%-89%)	12% (-7%-28%)	40% (4%-63%)	-16% (-80%-26%)	16% (-50%-53%)	-20% (-92%-25%)	-10% (-64%-26%)
PAPERS:											
McLeod 1945				PP							
Austrian 1976	IPD/PP	IPD/PP			IPD/PP		IPD/PP	IPD/PP			
Smit 1977					PP		PP				
Riley 1977	IPD	IPD		IPD	PP		IPD				
Austrian 1980	IPD	IPD		PP		PP	PP				
Kaufman 1947				IPD/PP							
Gaillat 1985	IPD		IPD	IPD/PP		PP	IPD	IPD	IPD/PP		IPD/PP
Klastersky 1986	IPD/PP		IPD/PP	IPD/PP		IPD/PP	IPD/PP	IPD/PP		IPD/PP	IPD/PP
Simberkoff 1986	IPD/PP		IPD/PP	IPD/PP		PP	IPD/PP	IPD/PP		IPD/PP	IPD/PP
Leech 1987	IPD		IPD	IPD		IPD		IPD		IPD	IPD
Davis 1987	IPD/PP		IPD/PP	PP				PP		PP	PP
Koivula 1997						PP		PP	PP		
Ortqvist 1998						IPD/PP	IPD/PP	IPD/PP		IPD/PP	IPD/PP
Honkanen 1999									IPD/PP		IPD/PP
French 2000						PP					

LRG=low risk group (i.e. healthy elderly); HRG=high-risk group; [a]Proportion in the HRG>50%; [b]Proportion in the HRG>20%; IPD=invasive pneumococcal disease; PP=pneumococcal pneumonia

The level of protection against IPD among the general elderly population (65%) was similar to that reported in previous meta-analyses (Hutchinson et al., 1999;Moore et al., 2000;Cornu et al., 2001) , i.e. previous estimates ranged between 66% [52% to 76%] and 82% [66% to 91%] (Table 4.2). Previous meta-analyses of VE in high-risk groups also appeared to confirm the findings presented here, i.e. estimates of vaccine efficacy are low and non-significant (Fine et al., 1994;Moore et al., 2000;Cornu et al., 2001). Fine and colleagues (1994) failed to demonstrate a protective effect against IPD in high-risk elderly, VE=-23% [-449% to 72%], whereas Moore and colleagues (2000) showed a slightly higher, although non-significant, level of protection against IPD, 47% [-94% to 86%]. The latter included in their analysis three fully randomised clinical trials performed among the elderly with underlying chronic conditions or with a history of community-acquired pneumonia but did not consider the randomised clinical trial that was performed among US veterans in 1987 and that did not demonstrate any efficacy, VE=-28% [-153% to 35%]. Cornu and colleagues (2001) found similar estimates of vaccine efficacy to Moore and colleagues (2000) when considering a subgroup of patients over 55 years old, VE=42% [0% to 82%].

4.4.3 Sensitivity analysis

A sensitivity analysis on the level of protection of the PPV was performed using, initially, a less conservative type of model and then different inclusion criteria with regards to the randomisation process and the study design. Estimates of vaccine efficacy against pneumococcal diseases, which consisted of both pneumococcal pneumonia and IPD cases, in high and low risk elderly were also derived.

For the effect sizes that were produced here, there was no evidence of significant between-study variation, and the two methods produced almost overlapping results (Table 4.3). If only randomised controlled trials were considered, the power to detect an effect was significantly reduced as the largest trial used a quasi-randomisation technique (Honkanen *et al.*, 1999). For the general elderly this left only one and zero trials respectively for pneumococcal pneumonia and IPD. For mixed elderly populations, the removal of the

QRCT had little impact on estimates of vaccine efficacy, though it further reduced the precision of the results (Table 4.3).

Table 4.3 - Sensitivity analysis of the results

	No. of studies	OR, random effects model [95% CIs]	OR, fixed effects model [95% CIs]	Chi-square (d.f.); P-value
All RCT & QRCT				
Pneumococcal pneumonia				
- Low risk group (LRG)	3	0.84 [0.47-1.50]	0.96 [0.70-1.30]	5.11(2); 0.078
- Mixed risk group (MRG)	6	1.04 [0.68-1.59]	1.09 [0.81-1.46]	7.12(5); 0.212
- High risk group (HRG)	4	1.20 [0.75-1.92]	1.19 [0.75-1.89]	2.22(3); 0.527
Invasive pneumococcal disease				
- Low risk group (LRG)	2	0.35 [0.08-1.49]	0.34 [0.08-1.48]	0.03(1); 0.857
- Mixed risk group (MRG)	6	0.56 [0.21-1.45]	0.54 [0.23-1.30]	3.57(5); 0.613
- High risk group (HRG)	4	0.80 [0.22-2.88]	0.73 [0.24-2.20]	2.84(3); 0.418
Only RCT				
Pneumococcal pneumonia				
- Low risk group (LRG)	1	0.85 [0.50-1.43]	0.85 [0.50-1.43]	-
- Mixed risk group (MRG)	4	1.20 [0.75-1.92]	1.19 [0.75-1.89]	2.22(3); 0.527
Invasive pneumococcal disease				
- Low risk group (LRG)	0	n.a.	n.a.	-
- Mixed risk group (MRG)	4	0.80 [0.22-2.88]	0.73 [0.24-2.20]	2.84(3); 0.418
Inclusion of Kaufman study (1947)				
Pneumococcal pneumonia (LRG)	4	0.58 [0.27-1.26]	0.60 [0.48-0.76]	24.63(3); <0.01
Invasive pneumococcal disease (LRG)	3	0.23 [0.12-0.46]	0.23 [0.12-0.46]	0.39(2); 0.825
Inclusion of Davis study (1987)				
Invasive pneumococcal disease (HRG)	5	0.97 [0.29-3.18]	0.88 [0.32-2.43]	3.47(4); 0.483
Inclusion of CCS				
Invasive pneumococcal disease (LRG)	7	0.53 [0.40-0.70]	0.55 [0.45-0.67]	6.57(6); 0.363
Invasive pneumococcal disease (HRG)	6	0.48 [0.29-0.80]	0.50 [0.39-0.65]	5.61(5); 0.346
Two endpoints together				
- Low risk group (LRG)	3	0.79 [0.45-1.42]	0.91 [0.67-1.23]	5.19(2); 0.074
- High risk group (HRG)	5	1.10 [0.72-1.70]	1.11 [0.72-1.70]	2.78(4); 0.595

RCT=randomised controlled trials; QRCT=quasi-randomised controlled trials; d.f.=degree of freedom; n.a. = not available; CCS = case-control studies

Although the study by Kaufman and colleagues (1947) appeared methodologically weak, its effect on the pooled estimates was assessed. Including this study in our analysis results in an estimated vaccine efficacy of 42% [-26% to 73%] against pneumococcal pneumonia (i.e higher but still not significant) and 77% [54% to 88%] for IPD (i.e. slightly higher with significant 95%CIs). Moreover, the single bacteraemic terminally ill patient reported by Davis and colleagues, was also included in the overall calculation of VE against IPD in HRG, and the final estimate dropped to a very low level with extremely wide confidence

intervals 3% [-218% to 71%]. Similarly, the level of protection of the vaccine fell considerably when the two final endpoints were analysed together, VE= 21% [-42% to 55%] in healthy elderly and a VE=–10% [-70% to 28%] in high-risk elderly.

Vaccine efficacy estimates from case-control and indirect cohort studies (Shapiro & Clemens, 1984;Bolan G *et al.*, 1986;Forrester *et al.*, 1987;Sims *et al.*, 1988;Shapiro *et al.*, 1991;Butler *et al.*, 1993;Farr *et al.*, 1995), also including elderly, have generally ranged around 50-80% for invasive pneumococcal disease (Table 4.4). Only one study showed no effect when looking at healthy or high-risk adults (30+), and elderly patients (55+) (Forrester *et al.*, 1987). When looking at the impact that all case-control studies had on our estimate of VE against invasive pneumococcal disease, a decrease on the level of protection of PPV is observed in the low risk elderly, VE=47% [30% to 60%], whereas a significant and higher estimate of VE is produced in the high-risk group VE=52% [20% to 71%]. Indeed, examining the funnel plots (Figure 4.3), it seems that there may be evidence of bias in studies of high-risk elderly, as the case-control studies tend to give higher estimates of vaccine efficacy (lower Odds Ratios) than the randomised controlled trials.

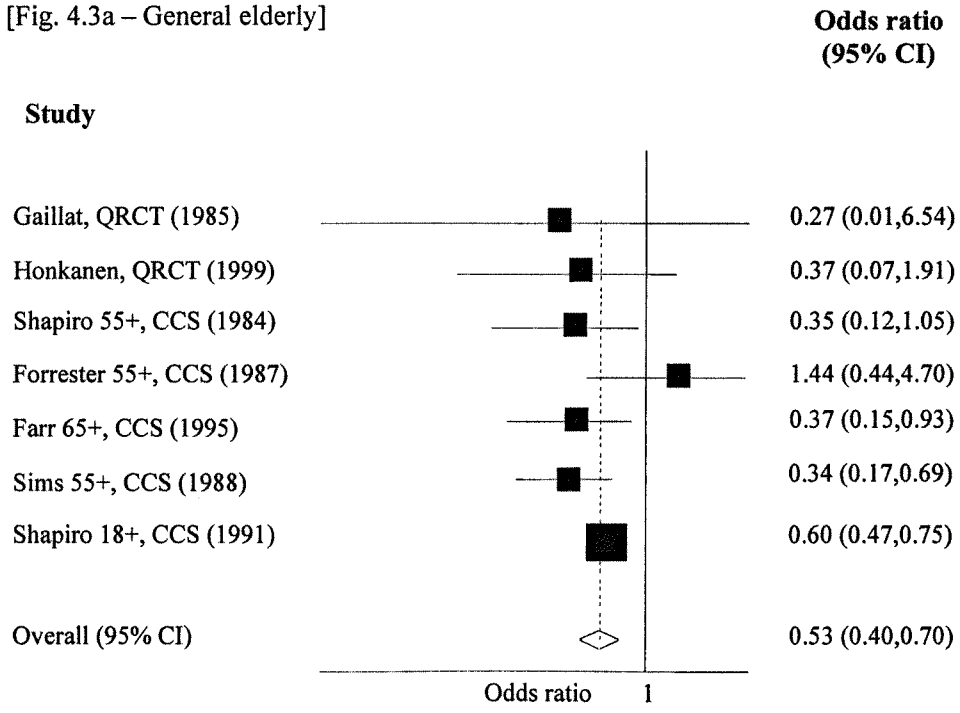
Table 4.4 – Case-control and indirect cohort studies of pneumococcal vaccine effectiveness in prevention of invasive disease

Reference	Study type	Setting	Population	Age (yrs)	Mean age cases (controls)	VE overall	VE in HRG	VE in Moderately Increased RG	VE in Mildly Increased RG
Shapiro *et al.*(1984)	Case-control study	Connecticut 1978-1982	Hospitalised patients: 90 cases and 90 controls	18+	62.1 (62.6)	67% (13%-87%)	0% (-1228%-93%)||	77% (27%-93%)**	70% (1% to 91%)***
Bolan *et al.*(1986)	Indirect cohort method	Canada May78-Mar84	Vaccinated invasive pneumo patients: 249; unvaccinated patients: 1638	2+	45 (45)	64% (33%-80%)		61% (1%-85%)^	
Forrester *et al.*(1987)	Case-control study	Denver (US) Sept.79-Mar.84	Hospitalised male patients: 89 cases 89 and controls	30+	64.7 (63.9)	-21% (-221%-55%)	-67% (-1465%-80%)*	-23% (-530%-71%)**	0% (-7743%-96%)***
Sims *et al.*(1988)	Multicentre case-control study	Pennsylvania Jan.80-Jul.86	Hospitalised patients: 122 cases and 244 controls	55+	70.1 (69.2)	70% (37%-86%)			
Shapiro *et al.*(1991)	Case-control study	Connecticut, 1984-1990	Hospitalised patients: 1054; hospitalised controls:1054	18+	67.6 (67.6)	56% (42%-67%)	21% (-55%-60%)#	61% (47%-72%)##	
Butler *et al.*(1993)	Indirect cohort method	United States, May.78-Apr.92	Vaccinated invasive pneumo patients: 515; unvaccinated patients: 2322	2+	57 (50)	57% (45%-66%)	49% (22%-67%)||	49% (23%-65%)|||	75% (57%-85%)||||
Farr *et al.*(1995)	Matched case-control study	United States, Jan 81-Dec87	85 cases, 152 controls	2+(~) or 65+		81% (34%-94%)			

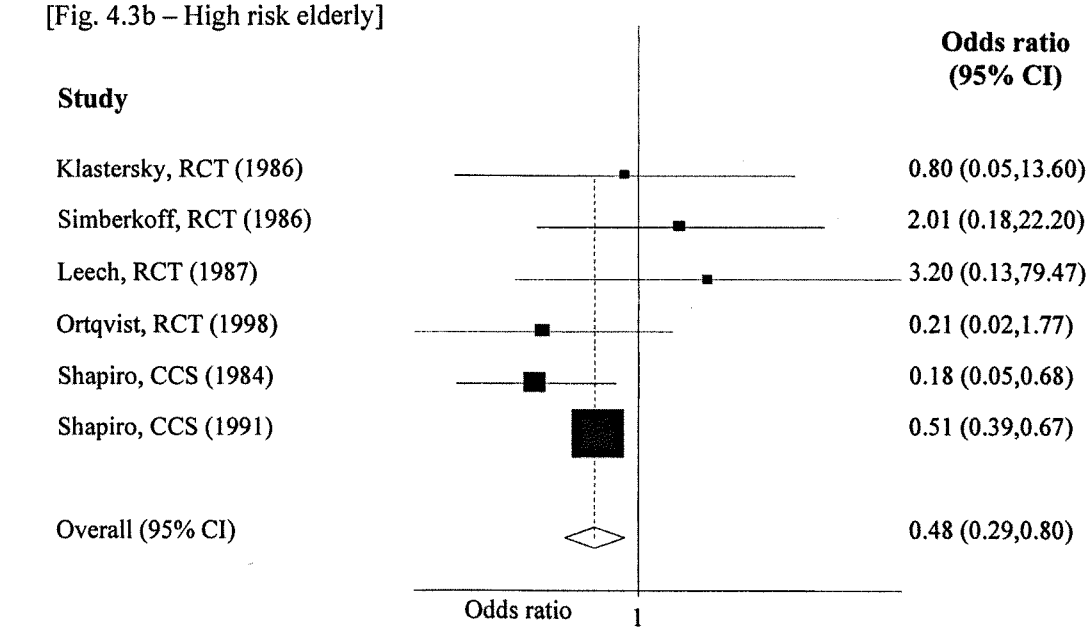
NOTE: HRG=high-risk group; RG=risk group; ^ includes patients (65+) with atherosclerotic cardiovalscular disease, congestive heart failure, COPD, asthma, diabetes mellitus, and no underlying disease; * calculated on patients with immunosuppressive conditions, asplenia, dysglobulinemia, renal transplantation, nephrotic syndrome; ** increased risk of pneumococcal infection: chronic pulmonary disease, alcoholism, diabetes mellitus, renal failure, congestive heart failure, liver disease; *** 55+ years of age and none of the above conditions; # Disseminated cancer, lymphoma, splenectomy, multiple myeloma, lupus erythematosus, leukaemia or myelodyspplasia; ## 55+, chronic alcoholism, congestive heart failure, diabetes mellitus; || including sickle cell anaemia, anatomic asplenia, dysgammaglobulinaemia, haematological, and several other immunocompromising conditions (sickle cell disease, anatomic asplenia, leukaemia, Hodgkin's disease, lymphoma, multiple myeloma, chronic renal failure, nephrotic syndrome, history of organ transplant...); ||| 5+ years of age with chronic but not immunocompromising illnesses (diabetes mellitus, atherosclerotic coronary vascular disease, congestive heart failure, COPD, asthma, alcoholism, cirrhosis), and those aged 65+ without underlying illness; |||| patients 65+ years of age; ~ 2+ and chronic condition OR just 65+.

Figure 4.3 – Published odds ratios (RCT, QRCT, CCT) and associated 95%CI for invasive pneumococcal disease.

[Fig. 4.3a – General elderly]



[Fig. 4.3b – High risk elderly]



RCT=randomised controlled trial; QRCT=quasi-randomised controlled trial; CCS=case-control studies

4.5 Discussion

The purpose of this chapter was to review the published estimates on VE of the polysaccharide pneumococcal vaccine and to perform a meta-analysis in order to predict the level of protection among the general elderly population and elderly at a higher risk of infection because of the presence of other diseases. These two groups of individuals were at the centre of the debate on whether to extend the vaccination programme to include healthy elderly, as has been done in the UK for the influenza vaccine. Randomised and quasi-randomised clinical trials were taken into consideration and previous meta-analyses were presented and discussed in order to understand the different results. Due to the small sample size of most of the trials, very wide confidence intervals were estimated for individual studies as well as for the overall pooled estimate.

The results of the meta-analysis, when taken with the findings of other meta-analyses and observational studies, showed that PPV offers a reasonable degree of protection in the general elderly population against invasive disease and a moderate effect in the high-risk elderly. The vaccine appeared to have little or no effect against pneumonia.

In the process of selecting the studies and extracting the data, a number of difficulties have arisen, first of which is related to the small number of methodologically strong (Jadad score>3) studies that satisfied the inclusion criteria and, secondly, their lack of power in detecting any effect of the vaccine. For these reasons, and also because of the wish to obtain comparable results to previous meta-analyses, it was decided to include all the studies that satisfied the inclusion criteria, whatever their Jadad score was, and to use meta-analysis so that the final estimate of vaccine efficacy would have more power. Furthermore, as diagnostic methods were not consistent throughout the papers, as well as the separate counting of the number of pneumococcal pneumonia and IPD cases, it was crucial that the two reviewers extrapolated the data separately and then cross-checked them with previous studies and reviews. The different inclusion criteria adopted for each study population and the variable definition of high-risk patients, represent another limitation of the analysis. We tried to take

this into account by selecting those studies that were most similar in term of place (all studies are in developed countries), age of the participants and their risk conditions.

Further studies would clearly help clarify whether the vaccine has any effect in these risk groups, and/or on non-invasive pneumonia. It is debateable, however, whether the additional expense of performing these studies would be cost-effective, particularly as the conjugate vaccine may be effective even in immunocompromised patients. A lack of efficacy against pneumonia does not necessarily preclude the use of the vaccine in the general elderly population. Recent economic evaluations have suggested that the vaccine may be cost-effective in these groups even though its efficacy is limited to invasive disease (Sisk *et al.*, 1997;Ament *et al.*, 2000). The following chapter (Chapter 5) will aim to evaluate the economic acceptability of the alternative vaccination programmes with PPV in the UK. This will be informed by the overall estimates of vaccine efficacy that have been derived in this chapter, and the estimates of the burden of disease gained in Chapter 3.

CHAPTER 5 - COST-EFFECTIVENESS ANALYSIS OF THE PNEUMOCOCCAL POLYSACCHARIDE VACCINE AGAINST INVASIVE PNEUMOCOCCAL DISEASE AMONG THE ELDERLY IN ENGLAND WALES

5.1 Aims

- To determine the costs associated with treatment of pneumococcal disease in the elderly;
- To develop a cohort model to estimate the reduction in the burden of disease attributable to the PPV vaccination programme;
- To investigate whether extending the vaccination strategy to include the healthy elderly would be a cost-effective policy from the health payer perspective.

5.2 Introduction

The resources available to the health care system are limited and so choices must be made concerning how to best allocate them among possible alternatives. Economic evaluation is a tool that can be used by decision makers to help allocate scarce resources. New medical interventions must be shown to be safe and effective (Black *et al.*, 2000) to justify their introduction. Increasingly, they also have to be shown cost-effective (Salisbury *et al.*, 2002).

In particular, the introduction and the implementation of a new vaccination programme is usually a long process, that requires a pre-licensing evaluation of the vaccine (Phase I-III), the definition of a vaccination programme - aims, strategy and coverage targets – as well as a post

licensing evaluation phase which should monitor the short and long term effects of the vaccine in the population (Begg & Miller, 1990). In addition, economic analysis and mathematical modelling should be carried out to deal with both direct and indirect costs and consequences of activities and, thus, to ensure optimal vaccine delivery (Drummond *et al.*, 1997;Salisbury *et al.*, 2002).

As discussed in Chapters 2 (section 2.4.1) and 4, PPV has been available for a number of years and, at the time of this analysis, was recommended to individuals at higher risk of pneumococcal infection. Although a number of economic evaluations had been performed for other European countries (Ament *et al.*, 2000;Postma *et al.*, 2001) as well as for the US (Gable *et al.*, 1990;Rose *et al.*, 1993;Sisk *et al.*, 1997;Nichol *et al.*, 1999;Weaver *et al.*, 2001;Pepper & Owens, 2002) and generally found that pneumococcal vaccination of the elderly population is relatively cost-effective and potentially cost-saving to the health care sector and to society, no such analysis had been performed for England and Wales when possible changes to the PPV programme were being discussed.

The aim of this chapter is thus to assess the costs and the health effects of vaccination with the 23-valent polysaccharide pneumococcal vaccines in England and Wales and to determine whether the current (at the time of the analysis) UK recommendation is a cost-effective programme from the public health perspective. As the vaccine does not confer protection against pneumococcal carriage (Chapter 2), the indirect effects of the vaccination programme are negligible and are not included in this analysis. The content of this chapter has been published (Melegaro & Edmunds, 2004b).

5.3 Background

5.3.1 Conducting an economic analysis

The establishment of the economic evaluation as one of the tools for decision-making in healthcare has lead to the development of standardised procedures and guidelines which have been published and that are now considered an essential requirement for sound and applicable analysis (Drummond *et al.*, 1997;Sculpher *et al.*, 2001;Claxton *et al.*, 2002;Spier, 2002). In particular, in conducting an economic analysis, the following steps should be considered: define the question, decide which type of analysis to use, establish the perspective (viewpoint) that will be adopted and, finally, compare methods and results to other published works. These aspects are described in detail below.

5.3.1.1 Defining the question

The definition of the question(s) to be addressed is clearly the first step. For example, which alternatives are being compared? In this case, the general question was: 'What are the costs and consequences of vaccinating the elderly at high risk of pneumococcal infection compared to the alternative of treating cases as they arise?' and 'What if the at-risk group is extended to include also healthy elderly?'.

5.3.1.2 Type of analysis

Three major economic techniques are available to perform economic evaluation, which differ in the measurement of the *consequences* of a course of action. These techniques, well described in Drummond (1997) and in a previous work by Torrance (1986) are: *cost-effectiveness analysis*, *cost-utility analysis*, and *cost-benefit analysis*. Which one to choose, generally depends on the question(s) that is asked. *Cost-effectiveness analysis* (CEA) measures the outcomes of a programme in terms of natural units (cases or death averted, life-years gained, etc.) and compares it to the cost of the intervention to determine the cost-effectiveness ratio (cost per case averted, cost per life year gained). *Cost-utility analysis*

(CUA) is a special form of CEA in which the measure of the effect takes account of morbidity as well as mortality. Such measures include the disability-adjusted life years (DALYs) or, more commonly, quality-adjusted life years (QALYs) gained. The advantage of CUA over CEA is that each year of life gained is weighted by its utility or health related quality of life measure (on a scale 0-1), so that different conditions and interventions can be compared. *Cost-benefit analysis* (CBA) determines the net societal benefit of the programme by placing a monetary value on the outcome and subtracting the monetary costs from the monetary benefits.

Cost-effectiveness analysis is the most widely used method and this may reflect the difficulties and extra effort in assigning health related quality of life weights or monetary values to health outcomes. The economic evaluation analysis of PPV described in this chapter uses cost-effectiveness analysis for this reason, i.e. the lack of high quality data on the impact of invasive pneumococcal disease on health related quality of life in the elderly and individuals' willingness to pay to avoid it. In any case, due to the high CFR for IPD (see chapter 3), most QALYs lost due to this condition will arise from the reduction in life expectancy. Thus QALYs and life-years lost are likely to be similar.

5.3.1.3 Viewpoint

Possible viewpoints include that of the patient and family, the hospital, the health care sector, and the global or societal viewpoint (Torrance, 1986). Although the latter include a much wider range of indirect consequences and would be, in theory, the appropriate one for public policy decision-making (Torrance, 1986), policy makers are generally more concerned with the direct cost of an intervention to their department and, moreover, reliable estimates of the societal costs may be difficult to obtain and time-consuming. Therefore, the analysis in this chapter took the viewpoint of health care provider (NHS).

5.3.1.4 Measuring costs and consequences

The collection or estimate of all the costs and outcomes related to the intervention requires the use of a wide range of data sources and the assessment of the level of reliability for each of these. The level of uncertainty of both costs and consequences is a crucial aspect to be considered when performing an economic evaluation and sensitivity analysis should be conducted to assess the effect of changes in the parameters and assumptions (Briggs & Gray, 1999;Briggs, 1999). Sensitivity analysis may be conducted using the following three approaches: one-way sensitivity analysis, extreme scenario analysis, and probabilistic sensitivity analysis (Figure 5.1). Univariate and multivariate sensitivity analysis were performed here.

Moreover, the impact of an intervention is generally measured over a predefined time span, and models are frequently used to assess the impact of the interventions on the burden of disease. Two different types of model may be used when evaluating vaccination programmes: cohort (or static) models and transmission dynamic models (Edmunds *et al.*, 1999). Cohort models assume that the risk of disease (which may be age-specific) in the unimmunised is unchanged by the intervention. Changes in future disease incidence only result from direct vaccine protection, which results from the assumed levels of vaccine coverage and efficacy. However, some vaccination programmes may interfere with the transmission of the infection in the population and, thus, have indirect effects among unimmunised individuals. These would normally be expected to be beneficial to public health but can also be detrimental. A shift in the age distribution of infection after vaccination may lead to an increase in disease severity for some infections, or a replacement effect may occur with an increase in the prevalence of non-vaccine types as a consequence of vaccination. These indirect effects of vaccination can be estimated using a transmission dynamic model (Brisson *et al.*, 2002). Since PPV only protects against disease (i.e. no herd immunity effects are produced by vaccination), the cost-effectiveness analysis presented in this chapter is based on a static model.

Figure 5.1 - Sensitivity analysis

Alternative forms of sensitivity analysis - Definitions

One-way sensitivity analysis systematically examines the impact of each variable in the study by varying it across all plausible range of values while holding all other variables in the analysis constant at their "best estimate" or baseline value.

Extreme scenario analysis involves setting each variable to simultaneously take the most optimistic (pessimistic) value from the point of view of the intervention under evaluation in order to generate a best (worst) case scenario.

Of course in real life the components of an evaluation do not vary in isolation nor are they perfectly correlated, hence it is likely that one way sensitivity analysis will underestimate, and extreme scenario analysis overestimate, the uncertainty associated with the results of economic evaluation.

Probabilistic sensitivity analysis, which is based on a large number of Monte Carlo simulations, examines the effect on the results of an evaluation when the underlying variables are allowed to vary simultaneously across a plausible range according to predefined distributions. These probabilistic analyses are likely to produce results that lie between the ranges implied by one-way sensitivity analysis and extreme scenario analysis, and therefore may produce a more realistic estimate of uncertainty.

Information abstracted from Briggs & Gray (1999)

5.3.1.5 Comparison with other studies

It is important to compare the methods and results of studies that have asked the same or similar question. A number of studies have been performed to assess the economic acceptability of the PPV in the US and in various European countries (Table 5.1). Of these studies, most concentrated on Pnc bacteraemia or IPD as an outcome of interest and showed that the vaccination was a cost-effective policy from health care payer and societal perspective. Assuming, (probably erroneously, Chapter 4), that PPV is as protective against pneumococcal pneumonia as it is against IPD, Ament and colleagues (2000) suggested that the programme would be cost saving from the societal perspective. Two studies (Patrick & Woolley, 1981;Sisk *et al.*, 2003) looked at high-risk groups in their analysis though considered different outcomes (pneumococcal pneumonia and IPD) and different study populations (18+ and 50-64 years of age) to those being addressed here. Neither of them considered the different levels of protection of the PPV in the high-risk group. The section below provides details of the method used and on the measurement of specific parameters.

Table 5.1 – Published cost-effectiveness analyses of pneumococcal polysaccharide vaccine

Reference	Setting	Vaccine type	Analysis	Perspective	Primary endpoint	Study populations	Base Case VE	Economic Outcome** (Cost per LY/QALY^ gained)
Willems *et al.* (1980)	US	14-valent	CUA	Societal and health care payer	Pneumococcal pneumonia	2+ (65+)	80%	£2,626 (£547)
Sisk *et al.*(1997)	US	23-valent	CUA	Societal	Pneumococcal bacteraemia	65+	by age and time since vaccination	£5,252
Rose *et al.*(1993)	US	23-valent	CEA	Societal	IPD	30+ yrs., HIV+ adults	65% in uninfected patients; reduced by 20-90% in HIV+ patients	£1,592
Postma *et al.* (2001)	The Netherlands	23-valent	CEA	Health care payer	IPD and pnc related hospitalisations	65+	by age and time since vaccination*	£7,013
Patrick & Woolley (1981)	US	14-valent	CBA	Health care payer and *societal*	Pneumococcal pneumonia	18+ (high-risk categories)	62%	0.13 (0.338) and *0.77 (2.32)***
Ament *et al.* (2000)	Western Europe	23-valent	CUA	Societal	IPD and pnc pneumonia	65+	by age and time since vaccination*	IPD: £5,555-15,277; PP: Cost saving
Pepper & Owens (2002)	US	23-valent	CUA	Societal	Pneumococcal pneumonia	22+ (35+)	50%	£29,960 (£12,980)
Sisk *et al.* (2003)	US	23-valent	CUA	Societal	IPD	50-64 (50-64 HR group)	by age and time since vaccination*	£6,245 (£9,932)

CUA=cost-utility analysis, CEA=cost-effectiveness analysis, CBA=cost-benefit analysis, QALY=quality-adjusted life years; IPD=invasive pneumococcal disease; *Vaccine efficacy is based on estimates in Shapiro and colleagues (1991), which depended on age and time since vaccination;* ** Economic outcomes reported in brackets refer to the study population reported in brackets;* ^ cost per life year (LY) gained are used in CEA, whereas cost per quality adjusted life years (QALY) gained are used in CUA;* *** Benefits to costs ratio (a ratio >=1 is necessary to justify a programme).*

5.4 Methods

5.4.1 Analytical approach

A cost-effectiveness analysis was performed to determine the economic acceptability of PPV among the elderly at 65 years old. In particular, this analysis assessed the impact of widespread vaccination among high-risk elderly (which was the UK policy at the time of the analysis) as well as on the health benefits and costs that would derive from widening the PPV recommendations to include healthy elderly individuals in the at-risk categories. In the base-case the alternative programs were either one-off vaccination at 65 or treatment of invasive pneumococcal disease as cases occur. The perspective adopted was the one of the health care provider (NHS) hence the costs were limited to expenditures and savings within this sector, leaving the costs to society and the wider economy out of the analysis. Health outcomes were measured in terms of life-years gained (LYG) from vaccination. The Net Benefit of the program was also calculated by multiplying these LYG by their shadow price (Drummond *et al.*, 1997) (which was varied in the analysis) and then subtracting from this the costs of the program.

As discussed in section 5.3.1.4, the model did not take into account population dynamics as herd immunity effects derived from vaccination of the elderly, with a vaccine that does not appear to prevent carriage (Herva *et al.*, 1980), would be negligible.

Moreover, estimates of the optimum age to vaccinate were produced using incremental analysis (Drummond *et al.*, 1997), which calculates the incremental cost-effectiveness ratios (additional costs that one programme imposes over another divided by the additional benefits, i.e. life-years gained) for each successive alternative (one-off vaccination at different ages), from the least costly to the most. With the same technique, we looked at the incremental costs and benefits of introducing regular booster doses at specific intervals (5 and 10 years) and assessed what is the optimum interval for revaccination.

5.4.1.1 Cohort model

Two hypothetical cohorts - vaccinated and unvaccinated - were followed throughout their lives, and morbidity, mortality and discounted costs of eventual treatment were compared. Due to the differences between elderly with or without underlying risk conditions (in terms of incidence rate, responsiveness to the vaccine, duration of protection and background mortality rate) (Fine *et al.*, 1994;Rubins *et al.*, 1999;French *et al.*, 2000), the hypothetical cohorts were each divided into two distinct sub-groups: high-risk group (HRG) and non high-risk group (NHRG) (see below). Results for the overall general population were derived within the model, weighting outcomes and costs with the prevalence of high-risk people in the community.

Prevalence and life expectancy of HRG *vs.* NHRG. The Morbidity Statistics from General Practices (MSGP4) survey (see Chapter 3, section 3.3.1.3 for details) provided the prevalence and background life expectancy of the two risk groups. Patients in the survey were divided according to whether or not they consulted for one of the high-risk codes that were included in the PPV recommendation (Salisbury & Begg, 1996) (Table 5.2) and from this the proportion of high-risk individuals was estimated. Background mortality rates were calculated for the two groups and for the general elderly population from deaths recorded in MSGP4. Checks were made to compare the background mortality rate obtained from this survey to those derived from the 1991 Census.

Table 5.2- ICD-10 codes that were considered in the definition of HRG among hospitalised patients

Code description	ICD-9 Code	ICD-10 Code
Asplenia or severe dysfunction of the spleen (incl. sickle cell disease and coelic syndrome)	282.5-282.6, 289.4-289.5, 7590	D57; D73; Q89.0
Chronic renal disease or nephrotic syndrome	581, 582, 584, 585	N04; N18
Immunodeficiency or immunosuppression due to disease or treatment, including HIV infection at all stages	0420-0449, 140-208, 279	B20-B24; C00-C97; D80-D89
Chronic heart disease	393-398, 414, 416	I05-I09; I25; I27
Chronic lung disease	490-496	J41-J47
Chronic liver disease including cirrhosis	571-573	K70; K73-K74
Diabetes mellitus	250	E10-E14

5.4.1.2 Costs and discounting

All future benefits and costs were discounted at a constant rate (3% per annum for both in the base case as recommended in the US Panel on Cost-effectiveness (Weinstein *et al.*, 1996). Discount rates were varied in the sensitivity analysis to allow for the UK recommendation levels (6% per annum for costs and 1.5% for health benefits (Department of Health, 1995)).

5.4.1.3 Sensitivity analysis

Due to the uncertainty that surrounds many of the key parameters included in the model, univariate (one-way) and multivariate (probabilistic) sensitivity analyses were performed. For the multivariate analysis, the model was run 1000 times and on each occasion a random set of input parameter values were chosen by means of Latin Hypercube Sampling using the software @Risk 4.0 (Palisade Corporation, New York). In this way an outcome distribution was produced that gave the proportion of simulations in which the programme is cost-effective (Net Benefit>0) for different values of the maximum willingness to pay for a life-year gained. Uniform, triangular and normal distributions were assumed for input distributions (Table 5.4).

5.4.2 Estimating model parameters

5.4.2.1 Disease incidence

Age-specific incidence rates of IPD obtained from the national laboratory enhanced surveillance system (CDSC/RSIL) and from HES (any pneumococcal confirmed code) were very similar, especially in the elderly (section 3.4.3.1). Since it was possible to determine the risk status of patients from the latter database, where seven diagnostic fields are available to record possible co-morbidities, this data-source was used (rather than CDSC/RSIL) to generate base-case incidence estimates of IPD. Only HES data for the period 1995-1998 were available at the time of the analysis.

Data were extracted and cleaned as explained in section 3.3.1.2 of this thesis and then records were divided into two groups according to whether or not any of the high-risk ICD-10 codes presented in Table 5.2 were reported in any of the seven diagnostic fields. The presence of at least one of these codes categorised the patient as being at high-risk (the remainder being assumed to be non-high risk patients). Age-specific incidence rates were calculated using HES data and population estimates for England published by the Office of National Statistics for the same years and are shown in Table 5.3. The following age categories were considered: 65-69, 70-74, 75-79, 80-84, and 85+ years old. A uniform distribution for incidence was used in the multivariate analysis; lower and upper bounds were set at, respectively, the minimum and maximum values that were observed over the three years period in each age group (Table 5.4).

Table 5.3 - Base case parameters values and sources

Parameters	Age Groups 65-69	70-74	75-79	80-84	85+	Data source
Health outcomes						
Admission rate - HRG[a]	83	126	124	157	250	HES
Admission rate - NHRG[a]	11	17	21	33	82	HES
LOS per admission - HRG (days)	16	15	16	18	18	HES
LOS per admission - NHRG (days)	13	15	16	18	14	HES
High CFR – HRG	16%	18%	21%	24%	28%	HES
High CFR – NHRG	15%	18%	17%	24%	16%	HES
Low CFR – HRG	9%	8%	13%	20%	17%	HES
Low CFR – NHRG	9%	9%	11%	20%	10%	HES
Direct cost[b]						
Cost per GP consultation (£)	19	19	19	19	19	(Netten A & Curtis L, 2002)
Cost of initial treatment (£)	8	8	8	8	8	(British Medical Association, 2002)
Cost of inpatient day (£)	242	242	242	242	242	(Netten A & Curtis L, 2002)
Cost of intensive care (£)	1,103	1,103	1,103	1,103	1,103	(Department of Health, 2002)
Vaccine parameters[b]						
Cost of vaccine & delivery (£)	11.4	11.4	11.4	11.4	11.4	(British Medical Association, 2002)
Vaccine efficacy - HRG (%)	20	20	20	20	20	Chapter 4
Vaccine efficacy - NHRG (%)	65	65	65	65	65	Chapter 4
Duration of protection - HRG (yrs)	5	5	5	5	5	
Duration of protection - NHRG (yrs)	6.5	6.5	6.5	6.5	6.5	
Analysis						
Prevalence of HRG (%)	9.6	9.7	10.2	9.7	7.7	(McCormick A *et al.*, 1995)
Admitted to ICU (%)[b]	5	5	5	5	5	
Discount rate outcomes (%)[b]	3	3	3	3	3	
Discount rate costs (%)[b]	3	3	3	3	3	
Coverage (%)[b]	60	60	60	60	60	

[a]All rates are per 100,000 populations per year; [b]These parameters are not age dependent

Average lengths of inpatient stay were derived also from HES for the specified age groups. Although clear dissimilarities were not observed between high and low risk patients, specific levels were assigned to the two groups. Minimum and maximum levels that were observed during the analysed period (1995-1998) were used as lower and upper bounds in the multivariate analysis.

We assumed that each case of IPD would visit the GP and receive antibiotic treatment before hospitalisation. A proportion of the hospitalisations (5%) were admitted in the Intensive Care Unit (ICU) of the hospital. This percentage was varied in the univariate analysis.

5.4.2.2 Case fatality ratio

Due to the difficulty in determining whether a patient who dies *with* IPD died *of* IPD, age and risk specific case-fatality ratios (CFR) for IPD were calculated in two ways. First, all deaths among patients that were admitted to hospital who had a discharge diagnosis including any

IPD codes were assumed to have died of IPD (Scenario 1). This gives an upper estimate, as in many instances pneumococcal infection would not be the underlying cause of death as many of these patients also have other codes recorded (Chapter 3). A low estimate is produced when considering hospitalised patients that had only IPD codes recorded (Scenario 2). For these, IPD was the only reported clinical condition and, thus, the number of deaths among them was more likely the result of the pneumococcal infection they contracted. Risk-specific CFR were produced dividing the number of deaths by the number of admissions and adjusting by the proportion of deaths among high-risk individuals that was observed in Scenario 1. Lower and upper bounds were estimated looking at, respectively, the minimum and maximum level observed over the three years period for the two scenarios.

5.4.2.3 Vaccine parameters

Estimates of vaccine efficacy in high and non-high risk groups were derived as described in Chapter 4. Overall levels of protection of 65% and 20% were used for, respectively, non-high and high-risk group, although the confidence intervals were very wide. A range of 5-10 years of protection was found in the literature (Shapiro *et al.*, 1991;Ortqvist, 2001), although some evidence of a lower vaccine-induced immunity was detected in certain high-risk groups (Obaro et al., 1996b;Rubins et al., 1998). In our analysis, base case values of 6.5 and 5 years for, respectively non-high and high-risk individuals were adopted. Probability distributions were assigned to vaccine efficacy and duration of protection (Table 5.4). We assumed that adverse events following immunisation would be negligible (Fedson et al., 1999b), and were therefore ignored.

Table 5.4 - Input distribution for the multivariate analysis

		NHRG		HRG	
Input name	**Distribution**	**Minimum**	**Maximum**	**Minimum**	**Maximum**
Admission rate - 65-69 yrs[a]	Uniform	9.2	13.6	52.1	99.4
Admission rate - 70-74 yrs[a]	Uniform	14.2	19.4	78.6	153.6
Admission rate - 75-79 yrs[a]	Uniform	16.4	26.6	73.9	160.1
Admission rate - 80-84 yrs[a]	Uniform	25.9	40.0	86.3	209.0
Admission rate - 85+ yrs[a]	Uniform	49.3	112.7	109.4	348.9
CFR - 65-69 yrs (Scenario 1)	Uniform	13%	17%	15%	17%
CFR - 70-74 yrs (Scenario 1)	Uniform	14%	22%	15%	18%
CFR - 75-79 yrs (Scenario 1)	Uniform	15%	19%	20%	23%
CFR - 80-84 yrs (Scenario 1)	Uniform	22%	26%	17%	26%
CFR - 85+ yrs (Scenario 1)	Uniform	13%	22%	25%	31%
CFR - 65-69 yrs (Scenario 2)	Uniform	6%	11%	6%	12%
CFR - 70-74 yrs (Scenario 2)	Uniform	3%	12%	3%	11%
CFR - 75-79 yrs (Scenario 2)	Uniform	8%	12%	10%	15%
CFR - 80-84 yrs (Scenario 2)	Uniform	19%	24%	19%	24%
CFR - 85+ yrs (Scenario 2)	Uniform	8%	17%	14%	29%
LOS per admission - 65-69 yrs	Uniform	13.0	13.4	14.5	16.7
LOS per admission - 70-74 yrs	Uniform	13.6	15.4	14.1	14.8
LOS per admission - 75-79 yrs	Uniform	15.9	16.1	15.1	16.3
LOS per admission - 80-84 yrs	Uniform	17.7	18.3	17.0	18.7
LOS per admission - 85+ yrs	Uniform	12.4	17.3	16.9	19.6
Vaccine efficacy[b]	Normal	-49%	92%	-188%	78%
Duration of protection (yrs)	Triangular[c]	4	9	3	7

[a]All rates are per 100,000 populations per year; [b]95% CIs are displayed; [c] symmetric triangular distribution (mode of 6.5 and 5 years in, respectively, NHRG and HRG)

5.4.2.4 Cost estimates

The costs included were the ones of the primary health care (GP consultation and first blind treatment) and the hospitalisation costs. All costs are given in pounds sterling at year 2000 prices.

The unit cost of a typical GP consultation (£19) was taken from the Unit Costs of Health and Social Care (Netten & Curtis, 2002). The average initial treatment cost per case was estimated from the standard recommendations given in the British National Formulary (BNF) for antibacterial therapy (British Medical Association, 2002). The Formulary recommends erythromycin for the treatment of atypical pneumonia (7 days course, £9.26) whereas erythromycin plus cefuroxime (7 days course, £18.71) is recommended for severe community-acquired pneumonia of unknown aetiology. The initial blind therapy for a possible meningitis or septicaemia case was assumed to be respectively a single dose of benzylpenicillin (GP pack = £1.90), or aminoglycoside (£1.51) together with broad-spectrum

penicillin (£2.01). The mean cost of the treatment becomes £8.35. In the univariate sensitivity analysis initial blind treatment with ceftriaxone was also considered (£21.89, 2-g vial), which gave a mean cost of the initial GP treatment of £16.62.

The unit cost per inpatient day was taken from the same standard source (Netten & Curtis, 2002), using the price of a generic ward (£ 242) that is the average cost of a variety of specialties. The inpatient cost for the infectious disease and geriatric wards (£348 and £144) were used in the sensitivity analysis as the upper and lower limit. All these costs take into account the average nursing costs, cost of the bed, cost for investigations to ascertain a diagnosis and treatment costs. The average cost of a bed per day in the ICU was taken from NHS Reference Cost (£1,103) (Department of Health, 2002). Due to a lack of data, we ignored long-term care for sequelae of IPD. Thus cost-estimates are likely to be somewhat higher than is reported here, and our cost-effectiveness estimates will be conservative.

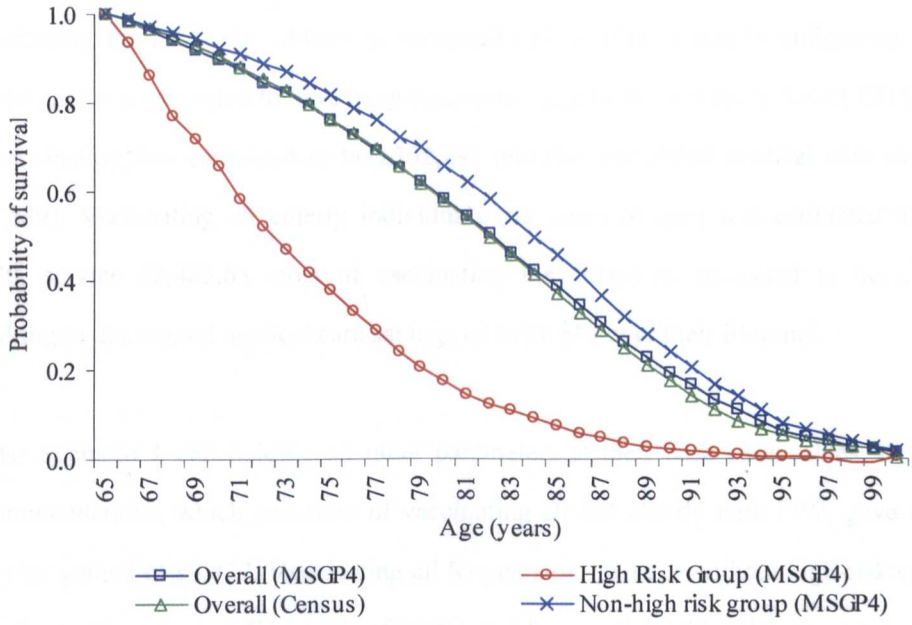
The cost of the vaccine (Pnu-Immune) was taken from the BNF (£9.94), whereas the delivery cost was set at £1.5, similarly to that used by Ament and colleagues (2000) in their base case analysis (3.00 ecu) (i.e. in the base case it was assumed that the vaccine would be given opportunistically, possibly with influenza vaccine). The overall cost of the vaccine for the base case was thus set at £11.44 and varied in the univariate sensitivity analysis. These unit costs were applied to the estimated outcome predicted by the model.

5.5 Results

5.5.1 Life-expectancy

From MSGP4 data, different background life expectancies were estimated for low and high-risk patients, with a probability of survival much lower in the latter case (Figure 5.2). Almost 10% of individuals over the age of 65 were found to have an underlying high-risk condition. The age specific percentages that were used in the model are reported in Table 5.3.

Figure 5.2 - Survival curves for elderly at different risk of infection.



Data taken from MSGP4 survey and compared with survival curve published by the Census.

5.5.2 Burden of invasive pneumococcal disease

From the base case analysis, around 3,000 invasive pneumococcal infections were estimated annually for England and Wales in 65+ years of age, and 34% have a discharge diagnosis indicative of being at high risk. From the MSGP4 survey around 10% of the elderly are high-risk, thus the incidence of IPD is roughly 3-4 times higher in HRG compared to NHRG. The overall average length of inpatient stay was estimated to be 11 and 13 inpatient days for non- and high-risk patients, respectively. Age specific figures are shown in Table 5.2. The estimated number of deaths attributable to IPD in 65+ years of age goes from an annual average of only around 50, if the low estimate of CFR is assumed (Scenario 2), to an annual average of roughly 500 deaths per year if the higher CFR is used (Scenario 1).

5.5.3 Cost-effectiveness results

5.5.3.1 Base Case Scenario

Vaccinating the HRG (i.e. elderly at increased risk of disease due to underlying morbidity conditions) was estimated to have a net discounted cost to the health service of £215,002 (cost of vaccination was estimated to be £302,291 and the discounted medical care savings was £87,289). Vaccinating all elderly individuals (65 years of age) was estimated to cost the health service £2,485,65 (cost of vaccinating the cohort is estimated to be £3,163,165 resulting in discounted medical care savings of £677,510 over their lifetime).

Under Scenario 1 and holding all other parameters at their base case values, the past UK recommendations, which consisted of vaccinating all HR elderly with PPV, gave a cost per life year gained of £9,477. Vaccinating all 65 years old, with or without high-risk conditions, is a dominating strategy (i.e. more effective and less costly) with a lower cost per life year gained of (£8,504) under base case assumptions. Higher estimates of cost per life year gained were reached when using the lower CFR (Scenario 2): £17,065 and £15,052 for, respectively, HRG and all 65 years old.

The optimum age at vaccination was determined ranking the different options, from the least costly to the most, and calculating the incremental expenditure and the additional life years that were gained switching from one option to the following (Table 5.5).

Table 5.5 - Incremental cost-effectiveness ratios for one-off vaccination policies at different ages.

Age at vaccination	Low CFR		High CFR	
	NHRG	HRG	NHRG	HRG
85	£3,362	£5,418	£2,077	£3,350
80	£5,140	£8,493	£7,110	£12,102
75	£27,911	£33,202	£11,633	£11,629
70	dominated	dominated	£13,168	£4,101
65	dominated	dominated	dominated	dominated

Alternatives that give fewer LYG with an increased expenditure are considered dominated options.

Assuming a maximum willingness to pay for an extra LYG of approximately £30,000, then the optimum age at vaccination, when higher values of CFR were considered, was 70 years old for both NHRG and HRG. Seventy-five years appeared to be the best option under the low CFR Scenario, although both incremental cost-effectiveness ratios were very close to what could be considered the maximum willingness to pay for an extra LYG. In Table 5.6 incremental cost-effectiveness ratios are shown comparing one-off vaccination at specific ages (65, 70, 75) to vaccination policies with booster doses every 10 years, and the latter with the option of revaccinating at shorter intervals (5 years). Incremental cost-effectiveness ratios below the level of £17,000 were estimated for both groups of elderly when revaccinating every 10 years and under the high CFR option. This value increased to £26,000 when considering the lower estimates of CFR. Much higher levels of incremental cost-effectiveness ratios were produced when looking at a revaccination policy every 5 years (£23,000-£61,000).

Table 5.6 - Comparisons of different vaccination policies. Incremental cost-effectiveness ratios.

	NHRG			HRG		
Age at vaccination:	**65 years**	**70 years**	**75 years**	**65 years**	**70 years**	**75 years**
Scenario 1 - High CFR						
Vaccination one off	£8,422	£6,143	£5,239	£9,477	£7,088	£7,584
Revaccination every 10 yrs	£14,602	£11,787	£10,438	£16,746	£13,897	£10,344
Revaccination every 5 yrs	£37,380	£35,328	£26,309	£29,085	£28,771	£23,680
Scenario 2 - Low CFR						
Vaccination one off	£14,886	£11,048	£7,589	£17,065	£13,930	£11,564
Revaccination every 10 yrs	£21,811	£15,473	£16,892	£25,663	£17,216	£16,714
Revaccination every 5 yrs	£61,310	£57,120	£32,188	£55,332	£46,459	£28,196

5.5.3.2 Univariate sensitivity analysis

In Table 5.7 the results of a univariate sensitivity analysis are reported under the two different scenarios. Apart from the CFR, the most influential parameter is the estimated incidence of IPD. Basing incidence on the primary discharge diagnosis only resulted in vaccination being unlikely to be deemed cost effective, regardless of mortality assumptions (£20,000-£54,000 per LYG). It is also apparent from Table 5.7 that if an extra GP consultation is necessary to vaccinate the elderly (instead of vaccinating opportunistically, presumably with influenza vaccine) then vaccination appears much less cost-effective (range £23,000-£52,000 per LYG).

Slightly higher levels of cost per life-year gained (range £10,000-£22,700) were also reached when the vaccine was assumed to prevent only the additional inpatient days caused by the bacteraemic episode (the average length of stay is from 2 to 3 days longer when looking at IPD compared to other non-invasive pneumococcal disease). Other important parameters include the discount rate: adopting the UK Treasury recommended discount rates means that vaccination becomes slightly more economically attractive than was shown in the base-case analysis (range £8,000-£16,800 per LYG).

Table 5.7 - Univariate sensitivity analysis. Cost per life-year gained of vaccinating elderly (65 years of age) with PPV

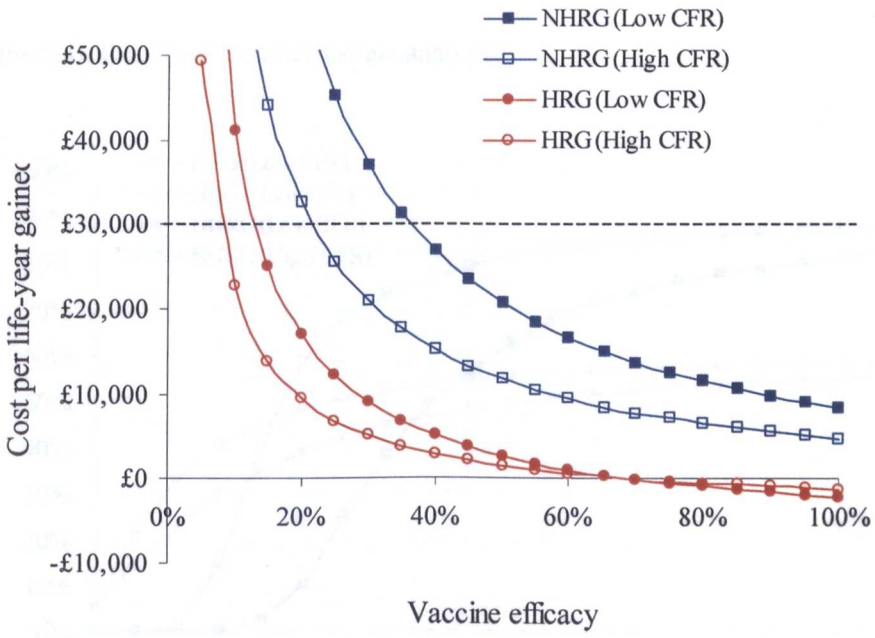
	Scenario 1 (High CFR)			Scenario 2 (Low CFR)		
	NHRG	HRG	ALL	NHRG	HRG	ALL
Base case values	**£8,422**	**£9,477**	**£8,504**	**£14,886**	**£17,065**	**£15,052**
Admission rate						
Only first diagnosis admissions	£19,616	£30,000	£20,277	£34,770	£53,999	£35,977
All diagnoses (SP codes + J181)	c.s.	c.s.	c.s.	c.s.	c.s.	c.s.
Intensive Care Unit						
Proportion to ICU = 20%	£7,437	£7,744	£7,461	£13,144	£13,945	£13,205
Proportion to ICU = 40%	£6,123	£5,434	£6,070	£10,822	£9,785	£10,743
Vaccine parameters						
Only protective against invasive part	£10,354	£12,604	£10,528	£18,300	£22,695	£18,635
Protection in HRG=3, NHRG=4 yrs	£12,522	£13,420	£12,596	£22,444	£24,007	£22,572
Protection in HRG=7, NHRG=9 yrs	£6,589	£7,725	£6,674	£11,504	£13,917	£11,679
Costs						
Costs per course of vaccination						
Only vaccine cost (£9.94)	£7,031	£7,730	£7,085	£12,427	£13,919	£12,540
Vaccine cost + GP consultation	£23,782	£28,764	£24,169	£42,034	£51,795	£42,779
Costs per inpatient day						
Infectious disease ward (£348)	£7,654	£8,126	£7,690	£13,528	£14,632	£13,612
Geriatric ward (£144)	£9,132	£10,726	£9,256	£16,141	£19,313	£16,383
Cost per GP cons & treat						
-25% of the base case	£8,426	£9,483	£8,508	£14,892	£17,075	£15,059
+25% of the base case	£8,418	£9,471	£8,500	£14,879	£17,054	£15,045
Average cost of GP treat =£16.62	£8,418	£9,470	£8,499	£14,878	£17,052	£15,044
Discount rate						
Benefits 6%, costs 6%	£14,786	£13,738	£14,690	£26,449	£24,658	£26,286
Benefits 0%, costs 3%	£5,215	£6,976	£5,333	£9,143	£12,568	£9,368
Benefits 1.5%, costs 6%	£8,264	£9,342	£8,347	£14,688	£16,808	£14,849

c.s. = cost saving

Figure 5.3 shows the sensitivity of the results to the different levels of protection of the vaccine in high and low risk elderly. Taking a maximum willingness to pay for a life-year gained of £30,000 (which has been suggested to be the National Institute for Clinical Excellence's upper limit (Devlin & Parkin, 2003)), for instance, then the model predicts that

provided vaccine efficacy is at least 10-15% then vaccination of the high risk would be cost-effective and 25-40% for vaccination of the non-high risk elderly to be cost–effective (holding other parameters at their base-case level).

Figure 5.3 – Cost per life-year gained by vaccine efficacy for high and low risk elderly.



Cost per life-year gained are shown under the two different assumptions on CFR.

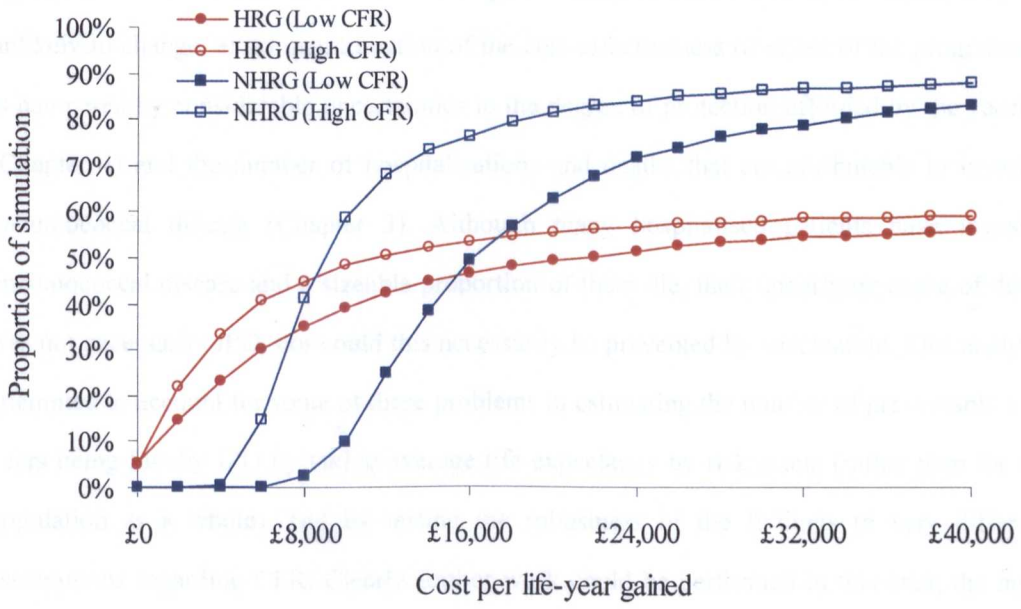
5.5.3.3 Multivariate sensitivity analysis

The results of the sensitivity analysis, in which all parameters except the discount rate (fixed at 3%) were varied probabilistically, are shown in Figure 5.4.

The figure shows the proportion of simulations that would be deemed cost-effective (positive net benefit) for different upper limits of society's willingness to pay for an additional life-year gained. Vaccination of high-risk groups leads to a relatively low proportion (no more than about 60%) of simulations being cost-effective regardless of which CFR is assumed and regardless of the society's willingness to pay for a life-year gained. This is because the

programme has a relatively low probability of being effective. On the other hand, when considering low-risk elderly, a higher proportion of simulations were cost-effective compared to HRG, unless the upper value that society places on a LYG is unrealistically low. The two different scenarios of CFRs are, nevertheless, influencing the rise of the curve and have a strong impact on the probability of having a positive Net Benefit in NHRG when the value of a LYG is around £15,000.

Figure 5.4 - Results of the multivariate analysis.



All the parameters are varied within their predefined distribution and the proportion of cost-effective simulations is shown for different values of a life year gained and for high and non high risk groups (respectively HRG and NHRG). CFR estimates are set to the lower or higher values.

5.6 Discussion

Invasive pneumococcal disease burden is high among the elderly and, in particular, among those considered to be at high-risk of pneumococcal infection. These individuals experience the highest incidence rates, and are those to whom the vaccine was recommended at the time of the analysis. In this chapter, an economic evaluation of the current 23-valent-polysaccharide vaccine against invasive pneumococcal disease was presented, looking at high-risk elderly and at the general elderly population. Although other analyses have been

published for other European countries (Ament *et al.*, 2000;Postma *et al.*, 2001;Ament *et al.*, 2001) as well as for the US (Gable *et al.*, 1990;Rose *et al.*, 1993;Sisk *et al.*, 1997;Nichol *et al.*, 1999;Weaver *et al.*, 2001;Pepper & Owens, 2002;Sisk *et al.*, 2003), this is the first study for England and Wales.

The previous UK recommendation is not likely to be the most cost-effective strategy, due to the low level of protection of the vaccine in these risk groups and the shorter life expectancy of elderly patients with chronic diseases. Routine vaccination of all elderly individuals appears to be more cost-effective. Although the relative ranking of these alternatives are unlikely to change, exact quantification of the cost-effectiveness of either of the programmes is hampered by considerable uncertainties in the degree of protection afforded by the vaccine (Chapter 4) and the number of hospitalisations and deaths that are attributable to invasive pneumococcal disease (Chapter 3). Although many hospitalised patients have invasive pneumococcal disease and a sizeable proportion of them die, their underlying cause of death was not necessarily IPD, nor could this necessarily be prevented by vaccination. This analysis attempted to account for some of these problems in estimating the number of preventable life-years being lost by IPD by taking average life expectancy by risk group (rather than for the population as a whole), and by testing the robustness of the findings to very different assumptions regarding CFR. Clearly further work could be performed in this area; the most valid and relevant information would be derived from a properly designed and implemented randomised clinical trial that was appropriately powered to investigate the effect of vaccination on mortality. This is unlikely to happen in the foreseeable future. Therefore, is there enough information currently available to make a reasonably sound judgement on the cost-effectiveness of vaccination of the elderly with PPV? Provided the vaccine is given opportunistically (at the same time as influenza vaccination, for instance) then it seems likely that vaccination of the non-high risk elderly population would be cost-effective by most criteria, simply because the vaccine is cheap, and the burden of disease is high. Vaccination of high-risk groups does not have a high probability of being deemed cost-effective, because the vaccine may not be effective in these individuals. It seems unlikely, however, that vaccination would be withdrawn from this group.

The incremental analysis suggests that the optimal age to vaccinate is 70-75 years depending on whether the, respectively, high or low CFR assumptions are adopted. This produces a lower gain in life expectancy as opposed to vaccinating at earlier ages (i.e. 65 years), but, at the same time, keeps at a lower level the costs associated with the programme. Our analysis also suggests that giving a booster dose of the vaccine every ten years could be an economically sensible policy to adopt as its additional cost per life-year gained still lies within the acceptable range.

The results of this and the previous chapter were presented at the JCVI, and partly contributed to the decision of recommending vaccination to all elderly individuals regardless of risk group (July 2003) (Chapter 2).

This chapter concludes a section that focused exclusively on the elderly population and that intended to investigate the effectiveness and cost-effectiveness of the pneumococcal polysaccharide vaccine. The PPV has been on the market and recommended to some at-risk categories for a number of years, although the levels of protections it confers and its economic acceptability had been frequently debated. The current availability of the pneumococcal conjugate vaccine, which appears to confer protection against both carriage and disease, even in the very young children, brings up new public health related questions on its direct and indirect effects and, as for the PPV, on the cost-effectiveness of alternative vaccination programmes. The following chapters will thus focus on these topics. Modelling as well as economic techniques will be used in order to gain insights into the pneumococcal conjugate vaccine and its effects at the population level.

CHAPTER 6 - PNEUMOCOCCAL TRANSMISSION IN HOUSEHOLDS: PARAMETER ESTIMATION AND MODELLING

6.1 Aims

- To gain insights into Pnc transmission dynamics in the pre-vaccination era;
- To estimate the duration of carriage and acquisition rate from the community and from infected family members in different age groups;
- To assess the importance of household *vs.* community transmission;
- To estimate the Secondary Attack Rate and Reproduction Number in households of different size and composition;
- To assess the importance of age and day care attendance as risk factors for pneumococcal carriage.

6.2 Introduction

As the majority of infected individuals remain asymptomatic, carriage data are needed in order to gain an indepth understanding of the transmission dynamics in the pre-vaccination era. Longitudinal studies have been performed to gather insights into the pathogen's mechanism of carriage and transmission within hosts (Gray *et al.*, 1980;Aniansson G *et al.*, 1992;Ekdahl *et al.*, 1997;Syrjanen *et al.*, 2001;Coles *et al.*, 2001). In this type of study

individuals are swabbed at regular intervals, their carriage status is assessed and inference on their rate of acquisition and on the duration of carriage can be obtained.

One of the most extensive studies on the duration of pneumococcal carriage was carried out by Ekdahl and colleagues (1997) who found an inverse relationship between duration of carriage and age among Swedish patients with clinical infections (diagnosed as pneumonia and acute otitis media) carrying penicillin-resistant pneumococci. Confirming previous work by Smith and colleagues (1993) who found great dissimilarities among the serotypes both in terms of acquisition and clearance rates, the study by Ekdahl and colleagues (1997) found serotype-specific durations of carriage. The authors, however, argued that this association was only due to age-specificity in the serotype distribution (i.e the types which showed longer duration were the ones that appeared to be more common in children, who typically carry the organism for longer). Similar results were found by Auranen and colleagues (2000), who fitted a transmission model to longitudinal data on pneumococcal carriage in Finnish families (FinOM Family study) taking into consideration transmission within the family and from the community and estimating acquisition rates and duration of carriage for children and adults.

Prospective longitudinal studies are, thus, particularly informative by following individuals for a period of time and recording their history of, for example, carriage acquisition as well as other personal information which may well be associated with the carriage episode (i.e. health status, living condition, day-care attendance). In the context of familial studies, such design might be of particular interest to assess the proportion of the data variability explained by within-individual variation or other sources of variation (Briollais *et al.*, 2003). However, the data arising from a longitudinal familial study have a complex correlation structure that cannot be modelled using classic methods for analysis of familial data at a single time point. The key feature of these correlated (or clustered) data is that items under study are bound together in sets (or clusters) that are known to the data analyst. For example, children in a day-care tend to cluster together (that is, respond alike), as do family members, and multiple measures on a single subject over time. This complexity of the data, however, can be an advantage, permitting more interesting, insightful analysis. Specifically, as Begg and Parides

(Begg & Parides, 2003) point out, 'in addition to studying how individual-level factors impact individual-level responses, clustered data allow us to study the effect of cluster-level factors on individual-level responses. Fuller, more thoughtful modelling of individual-level and cluster-level effects might enable us to exploit the data more completely, thereby leading us to better understand the sets of relationships that underlie important questions in medicine, public health and other domains'.

Longitudinal data are commonly analysed using one of three methods: marginal models, conditional models or transition models (Diggle *et al.*, 1994). Unlike marginal models and conditional (i.e.random-effects) models, which are focused on the correlation among response variables, a transition (Markov) model explicitly expresses the influence of past outcomes on the present outcome by modelling the conditional expectation of the response variable as a function of past outcomes and explanatory variables.

In this chapter a longitudinal dataset on pneumococcal carriage in UK families will be analysed and a first-order Markov model will be used to estimate pneumococcal transmission parameters. The approach that will be presented in this chapter represents a novel mathematical framework, whereby families (rather than individuals) are the unit of observation and the risk of infection is defined as a function of the number of other household members carrying the organism at a specific time point. Also, the model will account for possible unobserved events that may have occurred in between swabbing intervals.

Although serotype information was also collected in the study, the model that will be presented in this chapter will only consider pneumococcal carriage in general. An extension of this model will be provided in Chapter 7, where serotype-specific pneumococcal transmission parameters will be estimated. The chapter is divided into three parts. The first one provides a description of the available data, followed by a qualitative analysis on the age-related pattern of acquisition and carriage. In the second part of the chapter the model structure will be presented and results will be discussed. The third part will cover an extension of the model. In particular, the age specification of the model will be improved and possible

risk factors for pneumococcal carriage will be considered. The presentation of the longitudinal study and the descriptive analysis of the data can be found in Hussain and colleagues (2004a). The modelling work can be found in Melegaro and colleagues (2004).

6.3 Methods – The data

6.3.1 Description of the data

Data from a 10-month longitudinal follow-up study of pneumococcal carriage conducted in UK families were used. The study, which started on the 1st of October 2001 and ended in July 2002, was part of a EU funded project on pneumococcal disease (PncEuro) (Hussain *et al.*, 2004a;Hussain *et al.*, 2004b). The data consisted of follow-up measurements of Pnc carriage of pre-school children (<3 yrs.) and their families, which were enrolled through primary health care child registers of four general practices in Hertfordshire.

Following recruitment of a family, a study nurse administered a pre-tested structured, detailed questionnaire at the initial visit to each family member. Both household and individual data were gathered on potential risk factors or confounders including age, gender, education, day-care attendance, smoking, health status, population mixing in and out the house, any medication including antibiotics and household socio-demographic factors (type of house, number of rooms, parental occupation). A shorter questionnaire was administered at each monthly visit to each family member to gather information on any changes in individual and household details.

From each family member, a nasopharyngeal (NP) swab was obtained at initial home visit and followed by 9 further swabs at 4-week intervals. Sampling of absent members or members with illness was performed at a later date but within a 14-day period. Swabs were taken by a study nurse and transported to the Respiratory and Systemic Laboratory (RSIL) at the Specialist and Reference Microbiology Division (SRMD), HPA Colindale London within

24 hours. All NP samples were handled according to the Standard Operating Procedures of the WHO-Pnc trialists' network (O'Brien & Nohynek, 2003).

Data were collected on a standard case report form, which were doubled entered onto the database housed in CDSC. Laboratory data was entered on a laboratory form at RSIL and entered into a common database.

6.3.2 Data analysis

Descriptive data analyses were performed in Microsoft Excel. Confidence intervals on risk ratios were calculated using Taylor series in EpiInfo Version 6. The number of times a new serotype was introduced in the family was derived for different age groups. A new introduction was defined as the situation in which one family member was found to be carrying a serotype that was not present in that family at the previous test point.

6.3.3 Descriptive results of the PncEuro longitudinal study

6.3.3.1 Household

A total of 151 children in 132 families, representing 534 persons gave informed consent to take part in the study. Household relationship to the children included 132 mothers (24.7%), 125 fathers (23.4%), 101 siblings (18.9%) and 25 others including 3 grandparents.

Of the 132 initial families, 11 withdrew before the first visit and completion of the questionnaire. Of the remaining 121 families, more detailed household data indicated 21 families (17.4%) living in local authority-owned rental accommodation and 98 (81%) in owner occupied houses. Household size ranged from two to seven persons per house (mean and median of 4.0 persons/house). One hundred and six of these 121 families remained until the completion of the study (dropout rate 20%).

Of the 26 families that failed to complete the entire study, three immediately withdrew before completing the household questionnaire, four withdrew due to discomfort of nasopharyngeal swabbing, three had social reasons (i.e. family break-up) and the remaining 16 withdrew either due to inconvenience related to time involved or because they emigrated.

6.3.3.2 Individual

Demographic and health. In total 121 families (with 140 index cases) were visited at least once by the study nurse (representing a total of 489 individuals). The age and gender distribution of these children, their siblings and adult household members are summarised in Table 6.1 together with smoking, medication and vaccination history.

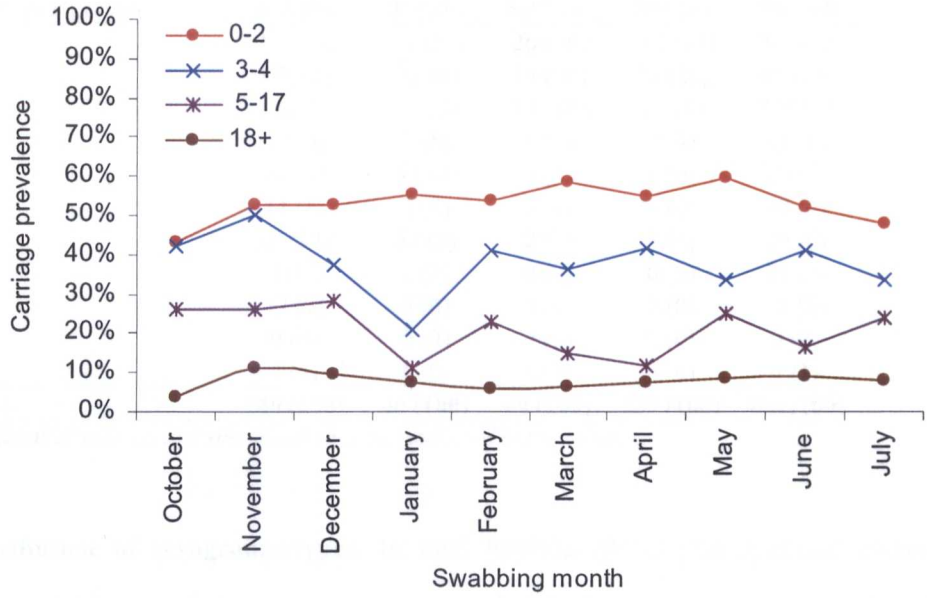
Table 6.1 Demographics of individuals in 121 'swabbed' households.

	Index cases (N=140)	**Siblings (<18 yrs) (N=109)**	**Adults (>18yrs) (N=239)**
Age in years (mean & range)	1.5 (0.3-3)	7.0 (3-18)	34.3 (18-72)
% female	55.8	49.1	52.3
% male	44.2	50.9	47.7
% at day-care	55.1	24.6	-
% at primary school	0	58.8	-
% at secondary school	0	14	-
% antibiotics past 12 mths	37.7	23.7	24.3
% smoking	0	0.9	23.7
% pnc vaccinated	0	0	0

n=488, 1 individual without age information

Prevalence of Pnc carriage. Nasopharyngeal swabbing was performed at least once in these 489 individuals with a total of 3767 swabs taken, representing 77% of the possible maximum. Overall 932 (25%) samples revealed pneumococcal carriage. At least one episode of pneumococcal carriage was noted amongst 112 of the 121 families swabbed (93%) over the study period. There were no significant seasonal differences in the prevalence of carriage by age group over the 10-month period (Figure 6.1) (t-test trend >0.05 for all age groups).

Figure 6.1 Pneumococcal carriage rates by age and swabbing month.



Rates are reported by age of the study participants at the start of the study and by month of swabbing (October 2001- July 2002).

Mean prevalence by age group over the entire study period ranged from 52% for 0-2 yr. olds, to 45% for 3-4 yr. olds, 21% for 5-17 yr. olds and 8% for those 18+ yrs. Children less than 5 years of age were significantly more likely than the older age groups (5+ years) to carry Pnc (RR=4.84, 95%CI: 4.25-5.51, $p<0.000001$).

Among all study participants, 282/489 (58%) individuals were found to be Pnc carriers at least once throughout the study period (Table 6.2). When stratified by age the proportion carrying Pnc at least once ranged from 86% in 0-2 year olds to 36% in those 18+ years of age. Indeed, among the 0-2 years old, 47% were found to carry Pnc at least 5 times during the study follow up time compared to 1% of those 18+ years of age.

Table 6.2 Number (%) of positive swabs per person and by age group.

Number of Pnc positive swabs per person	0-2 yrs	3-4 yrs	5-17 yrs	18+ yrs	Overall
0	19 (14)	10 (25)	26 (38)	152 (64)	207 (42)
1	17 (12)	7 (18)	19 (28)	51 (21)	94 (19)
2	14 (10)	7 (18)	10 (14)	22 (9)	53 (11)
3	13 (9)	3 (8)	6 (9)	9 (4)	31 (6)
4	12 (9)	4 (10)	3 (4)	1 (0)	20 (4)
5	11 (8)	3 (8)	3 (4)	1 (0)	18 (4)
6	19 (14)	5 (13)	2 (3)	3 (1)	29 (6)
7	10 (7)	1 (3)	0 (0)	0 (0)	11 (2)
8	12 (9)	0 (0)	0 (0)	0 (0)	12 (2)
9	9 (6)	0 (0)	0 (0)	0 (0)	9 (2)
10	4 (3)	0 (0)	0 (0)	0 (0)	4 (1)
Total	**140 (100)**	**40 (100)**	**69 (100)**	**239 (100)**	**488 (100)**

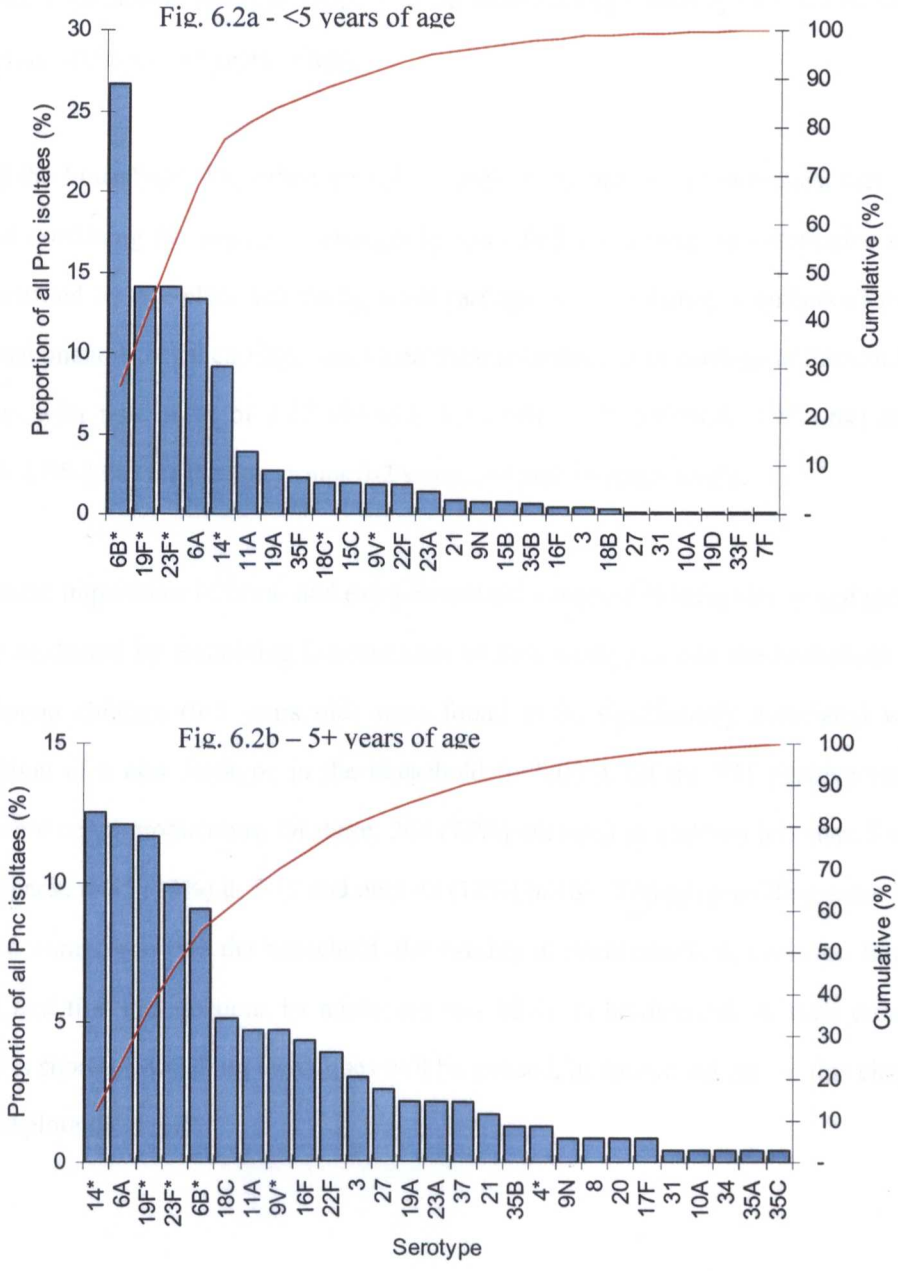
1 individual with no age specification is not included in the table

Distribution of serogroups/types. In total 901/932 (97%) pneumococcal isolates were serotyped (the remainder being non-capsulate). 34 distinct serotypes were found in the isolates. The 10 most prevalent serotypes comprised 90% of all isolates in the 0-5 years olds (Figure 6.2). The five most prevalent serotypes in this group were 6B (27%) followed by 19F, 23F, 6A and 14, accounting for 51% of the samples. Among the 5+ years old, serotypes 14, 6A, 19F and 23F were again the most frequent isolates with 6B less frequently found compared to <5 year olds (Figure 6.2)

Simultaneous carriage of more than one serotype in an individual at a particular time-point was only detected on six (0.16%) occasions. Five of these individuals were ≤5 years of age.

Antibiotic resistance. The proportion of isolates with any erythromycin resistance (alone or in combination) was 10% and the proportion with any degree of penicillin resistance (alone or in combination) was 3.7%. Cefotaxime resistance was noted in only 0.3%. The most common serotypes showing resistance to any of the three antibiotics were: serotypes 14 (45%, n=92), 19F (11%, n=128), 6B (14%, n=214) and 9V (17%, n=23). All of these serotypes are included in the 7-valent PCV.

Figure 6.2 Serotype frequency distribution among pneumococcal carriers.



*Serotypes marked with * are included in the 7-valent Pnc vaccine*

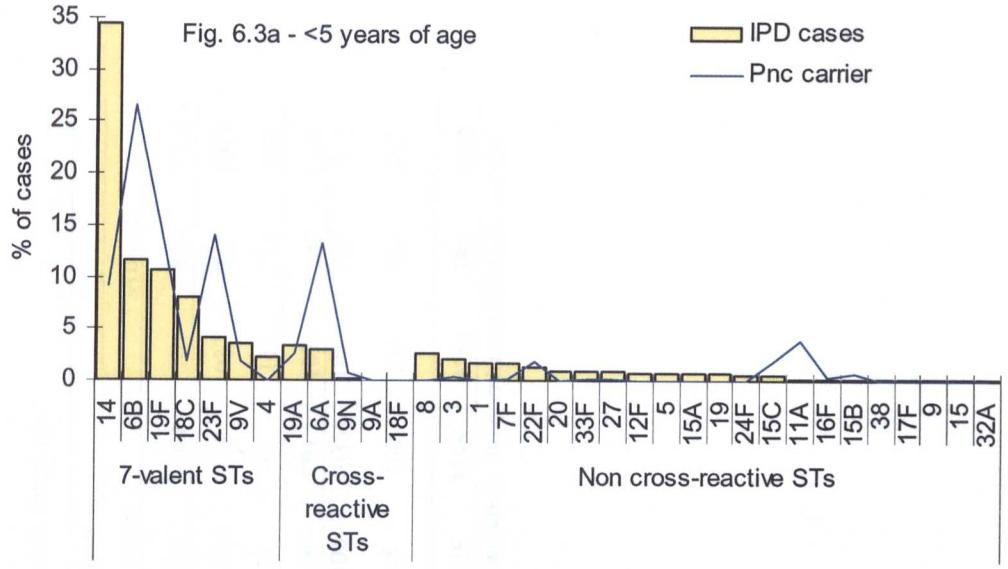
Comparison with invasive isolates. Comparison of the distribution of carriage serotypes with the distribution of invasive Pnc isolates in those under-5 year olds in England and Wales in year 2000 demonstrated large differences between serotypes (Figure 6.3). Serotypes 14, 18C, 9V, 4, 1, 8, 7F and 3 in particular seemed to be more likely to be invasive than carried.

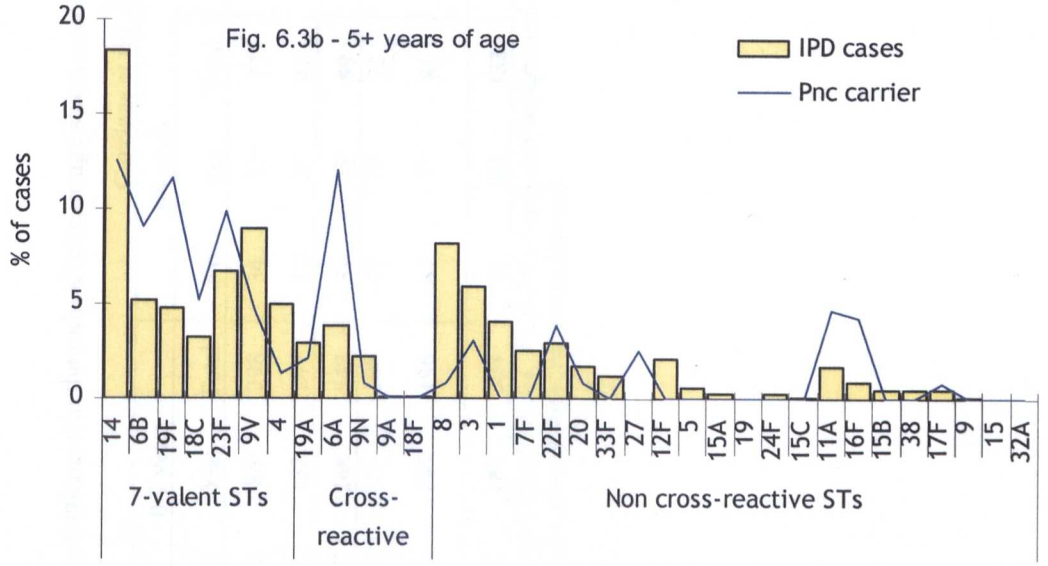
The latter four serotypes (1,8,7F and 3) are not covered by the 7-valent conjugate vaccine. The same non-vaccine serotypes appear to be more common among invasive isolates than among Pnc carriers in 5+ years of age.

Role of the household. The effect of within family exposure on pneumococcal carriage was assessed examining the number of changes in individual status over the observation intervals once stratified by age-class and background carriage in other family members (Table 6.3). Individual pneumococcal carriage was found to be associated with carriage in the other family members with risk ratios of 1.42 (95%CI: 1.26-1.61), 1.25 (95%CI: 0.95-1.64) and 2.25 (95%CI: 1.65-3.08) for the age groups 0-2 years, 3-4 and 5+ respectively.

The relative importance of intra- and extra-household exposure to infection by age group was initially evaluated by examining introductions of new serotypes into the household (Table 6.4). Young children (0-5 years old) were found to be significantly associated with the introduction of a new serotype in the household ($p<0.005$). Of the 931 positive tests, 353 (38%) were new introductions. Of these, 264 (75%) occurred in children less than 5 years of age compared to 45 (13%) in 5-17 and only 44 (12%) in 18+. Though providing some insights on first occurances within the household, the validity of these results is, however, limited by the fact that first introductions by adults are less likely to be detected, as their duration of carriage is shorter. Modelling techniques will be utilised, in the second part of this chapter, to further explore this topic.

Figure 6.3 Serotype frequency distribution: comparing IPD isolates with carriage study results.





IPD isolates as reported in the national surveillance system (CDSC/RSIL, 2000).

Table 6.3 The number of observed changes in the individual carriage status over the observation intervals.

Carriage in the other family	Individual carriage	Carriage at the next observation											
		0-2 years			3-4 years			5+ years			All ages		
		No	Yes	Total	No	Yes	Total	No	Yes	Total	No	Yes	Total
No other carriers in the family	No	212	86	298	34	23	57	686	58	744	932	167	1099
	Yes	65	182	247	17	25	42	36	11	47	118	218	336
Total		**277**	**268**	**545**	**51**	**48**	**99**	**722**	**69**	**791**	**1050**	**385**	**1435**
Other carriers in the family	No	65	43	108	47	25	72	935	100	1035	1047	168	1215
	Yes	52	144	196	44	37	81	115	45	160	211	226	437
Total		**117**	**187**	**304**	**91**	**62**	**153**	**1050**	**145**	**1195**	**1258**	**394**	**1652**

The table is stratified according to age class (0-2, 3-4, 5+ years of age) and background carriage in the family (no carriers/at least one carrier among the other family members at the start of the observation interval).

Table 6.4 Number of positive, negative, and tested samples by age.

	Positive test				
Age group	First introd. (%)	Ongoing/ Concurrent	All	All negative	Number of tests (%)
a. <1y	89 (25)	174	263	209	472 (13)
b. 1y	69 (20)	119	188	180	368 (10)
c. 2y	68 (19)	69	137	150	287 (8)
d. 3-4y	38 (11)	60	98	159	257 (7)
e. 5-17y	45 (13)	51	96	359	455 (12)
f. >18y	44 (12)	105	149	1779	1928 (51)
Total	353 (100)	578	931	2836	3767 (100)

Positive tests are stratified also according to whether it was a new introduction or if it was an ongoing or concurrent episode of carriage of a specific serotype (ongoing = the type was carried at the previous test point by either the same individual in the family or other family members; concurrent = someone else in the family is carrying the same type at the same time).

6.3.4 From individual level data to family data

The 121 families that were visited at least once by the study nurse and which comprised 489 individuals were considered in the following analysis, to estimate pneumococcal transmission parameters within the household (section 6.4). Although serotyping was performed when Pnc carriage was detected, this initial analysis considered pneumococcal carriage in general and, thus, only looked at whether or not the individual was carrying the bacteria. Moreover, as there were only six circumstances in which two serotypes were found in the same individual at the same time, the model was based on the assumption that simultaneous carriage of different serotypes is rare enough to ignore initially.

For each individual that took part in the study, the carriage status at each monthly visit was obtained from the data and then recoded as 0, if non-carrier, 1 if carrier and 9 when either the swab was not taken or the lab result was not reported. The household state at each visit was derived combining the carriage status of all the family members and resulted in a sequence of 0s and 1s if their information was complete. Missing information on at least one family member resulted in incomplete information at the household level and, thus, a missing value code. Family sequences were organised so that the last number represented the status of the youngest member of the family. Due to the strong association that has been shown in other studies (Ekdahl *et al.*, 1997;Auranen *et al.*, 2000) between pneumococcal carriage and age,

with younger children having a much higher prevalence and longer duration of carriage, a cut-off at 5 years of age was set and households were stratified by family size and composition (number of individuals <5 and 5+ years of age in the family). Strings of household results were derived, which were then converted into a table showing the number of transitions between each pair of household states over a 28-day period for each family size and structure (Table 6.5).

Table 6.5 –Example of a count of family transitions over a 28-day period.

Family status at time t	*Family status at time t+1*							
	000	*100*	*010*	*110*	*001*	*101*	*011*	*111*
000	85	0	2	0	23	1	0	0
100	0	0	0	0	0	0	0	0
010	3	0	1	0	2	0	0	0
110	0	0	0	0	0	0	0	1
001	22	0	3	1	51	2	4	1
101	2	0	0	0	4	3	1	0
011	1	0	0	0	6	1	2	0
111	2	0	0	0	1	1	0	0

Data extracted from from the Pnc-Euro study, families of 3 individuals with one child < 5 years of age.

Two households of 2 individuals and one of 7 were excluded from the analysis as their sequences were non informative. Ten distinct tables $N_{z,u}$ were derived for the available combinations of, respectively, household size (z) and number of adults (u) in the family: (3,1), (3,2), (4,2), (4,3), (5,2), (5,3), (5,4), (6,3), (6,4), (6,5). Only complete family transitions, where the infection state of all household members was known on two consecutive observations, were used in the following analysis.

As a previous study (Ekdahl *et al.*, 1997) suggested that duration of carriage might be less than 28 days, especially in adults, it was possible that not all episodes of carriage were observed from the data. This aspect was considered in the structure of the following model.

6.4 Methods - The model

Following the work by Auranen and colleagues on both Hib and Pnc infection (1996;2000) the model considered pneumococcal transmission within the household. Each individual is assumed to be either in a non-infected state, i.e. susceptible to infection (S), or already infected (carriers) (C) and, as a consequence, able to spread the infection to uninfected individuals in their household. No pneumococcal specific disease was observed so this possibility was not included. As in Auranen and colleagues (2000) the transition from C->S was set to be dependent on a age-dependent *recovery rate*, and the transition from S->C to be a function of the potential exposure to the infective agent both within the family (*within-family acquisition rate*) and outside the family (*community acquisition rate*).

The probabilities of transition from an infected to an uninfected state and vice versa in a short time interval δt were then defined for an individual in the age class i=1,2 (where 1=child (<5 years) and 2=adult (5+ years))

$$P_i\,(C \rightarrow S)_{\delta t} = \mu_i \cdot \delta t \qquad [6.1]$$

$$P_i(S \rightarrow C)_{\delta t} = \left(k_i + \frac{\beta_{i1} I_1(t) + \beta_{i2} I_2(t)}{(z-1)^w} \right) \cdot \delta t \qquad [6.2]$$

where μ_i and k_i are, respectively, the clearance and the community acquisition rates for age class i and z is the family size. $I_1(t)$ and $I_2(t)$ are the number of, respectively, infected children and infected adults in the family. β_{ij} is the transmission rate from an infected to an uninfected individual and it reflects both the infectiousness of an individual in the age class j and the susceptibility of an individual in the age class i. Thus the within household probability of being infected in δt is a function of the number and age class of the other family members that are carrying the bacteria at that particular time. Community acquisition rates and recovery rates are similarly defined in vectors: $[k_1, k_2]$ and $[\mu_1, \mu_2]$. The term $(z-1)^w$ in equation [6.2] represents a density correction factor; (z-1) being the number of other family members in families of size z and w the factor that controls the extent of density dependence. When w=0 the model reflects density independent transmission: the probability of contracting infection

from another specific individual in the family does not change with family size and, thus, the average number of contacts increases linearly with family size. When w=1 the probability of getting in contact with the same individual decreases in bigger families although the average number of contacts remain constant. If w>1 the average number of contacts decreases with family size. In total nine parameters define the model.

Equations [6.1] and [6.2] were used to derive the probability p_{rs} of transition between two different family states r and s in a short time interval δt. These probabilities were calculated for each household size and composition. It is assumed that in a short time interval δt, here chosen as 1 day, only one member of the household will change status (either through infection or recovery). The probability of transitions where more than one individual changes status is therefore set to zero. For example, in a family of size three composed of two adults and one child, the probabilities of going from state 001 (two susceptible adults and one carrier child) to states 000, 101 and 011 in one time step, are derived using respectively equation [6.1] to become a fully susceptible household and equation [6.2] to reach states 101 or 011. The $T_1(3,2)$ matrix, (equation [6.3] below), contains all the probabilities of transitions from the initial family status at the top of the matrix to the consecutive status given on the left hand side of the matrix when δt is 1 day.

The sensitivity of the model to changes in the definition of δt (1/2 day, 2 days) was checked. The daily probability that the family does not change state is given by $q_{rr} = 1-\Sigma_{s\neq r}p_{rs}$. Similar formulations of the *transition matrix* T_1 are expressed for families with 3 to 6 members and different age structures.

The families transition probabilities for a 28-day interval were then derived as $\mathbf{T_{28}(3,2)}=T_1^{28}(3,2)$. This allowed handling transitions in which more than one individual in the family changes status. Moreover, not having specified the pathway from one state to the next, unobserved events were implicitly included.

$$
T(3,2) = \begin{array}{c} \\ 000 \\ 100 \\ 010 \\ 110 \\ 001 \\ 101 \\ 011 \\ 111 \end{array}
\begin{array}{c}
\begin{array}{cccccccc} 000 & 100 & 010 & 110 & 001 & 101 & 011 & 111 \end{array} \\
\begin{bmatrix}
q_{11} & \mu_2 & \mu_2 & 0 & \mu_1 & 0 & 0 & 0 \\
k_2 & q_{22} & 0 & \mu_2 & 0 & \mu_1 & 0 & 0 \\
k_2 & 0 & q_{33} & \mu_2 & 0 & 0 & \mu_1 & 0 \\
0 & [2^{-w}\beta_{22} + k_2] & [2^{-w}\beta_{22} + k_2] & q_{44} & 0 & 0 & 0 & \mu_1 \\
k_1 & 0 & 0 & 0 & q_{55} & \mu_2 & \mu_2 & 0 \\
0 & [2^{-w}\beta_{12} + k_1] & 0 & 0 & [2^{-w}\beta_{21} + k_2] & q_{66} & 0 & \mu_2 \\
0 & 0 & [2^{-w}\beta_{12} + k_1] & 0 & [2^{-w}\beta_{21} + k_2] & 0 & q_{77} & \mu_2 \\
0 & 0 & 0 & [2^{1-W}\beta_{12} + k_1] & 0 & [2^{-w}(\beta_{22} + \beta_{21}) + k_2] & [2^{-w}(\beta_{22} + \beta_{21}) + k_2] & q_{88}
\end{bmatrix}
\end{array}
\qquad [6.3]
$$

Note that in the transition matrix above δt=1 day. All rates are per day.

6.4.1 Parameter estimation

Maximum likelihood techniques (Brown & Rothery, 1993;Williams & Dye, 1994;Hilborn & Mangel, 1997) were adopted to estimate the nine model parameters. This technique is broadly applicable to problems of parameter estimation. The basic idea of maximum likelihood is to find those values of the parameters for which the observed data are most likely to have occurred (Brown & Rothery, 1993). These parameter estimates are thus called maximum likelihood estimates (MLE). The log likelihood L(z,u) and saturated log likelihood $L^*(z,u)$ functions were derived from each monthly transition matrix $\mathbf{T}_{28}(z,u)$ and from the observed number of family transitions between states $n_{rs}(z,u)$. The deviance was then calculated for each family size and composition as follows:

$$\mathrm{Dev}_{z,u} = 2\cdot(L^* - L) = 2\cdot\sum_{r=1}^{2^z}\sum_{s=1}^{2^z} n_{rs}\left[\ln(n_{rs}) - \ln(P_{rs}N_r)\right] \qquad [6.4]$$

where n_{rs} is the number of family transitions observed in the data from state r to state s and $N_r = \sum_s n_{rs}$. The P_{rs} is the element rs of matrix $\mathbf{T}_{28}(z,u)$ or, in other words, is the model probability that a family of size *z* and with u adults moves from state r to state s in a 28 day interval. The upper limit of the summations represents the number of family states that are possible for each family size.

The overall deviance [6] is obtained as the sum over all family sizes and compositions

$$\mathbf{Dev} = \sum_{z=3}^{6}\sum_{u=1}^{z}\mathrm{Dev}_{z,u} \qquad [6.5]$$

Maximum likelihood estimates for the parameters are obtained by minimising the deviance.

The profile likelihood method (Armitage & Colton, 2004) was used to derive confidence intervals for the model parameters. The model was set up first in Microsoft Excel and then programmed in Matlab 6.5. The development of the programme in Matlab allowed more flexibility in the model structure and the possibility to include further information that was available in the dataset. More on this will be said in section 6.4.9 of this chapter.

6.4.2 Model fit

The overall fit of the model could not be formally assessed using a chi-squared test on the residual deviance and degrees of freedom. This was because the expected count for each cell was too small and usually less than one.

However, after aggregating the states with the same number of carriers, it was possible to assess the goodness of fit visually for each family size by plotting the number of family transitions between states and comparing it to the number obtained from the model after aggregating across cells. Chi-square tests comparing the observed and estimated number of transitions on the aggregated data were performed. Using the chi-squared test in this way only enables the detection of fairly large aberrations in the model fit because the fit is only being tested after aggregation of data and estimates from a more complex model.

6.4.3 Measures of transmissibility

Equation 6.2 gives the individual probability of being infected in the small time interval δt taking into account the number of infectious carriers in the same household and the age-specific transmission rates. Nevertheless, in order to assess the transmissibility of an infection inside a household, more specific measures are needed that also take into consideration each carrier's duration of infectiousness and, thus, give the number of new infections produced during that period.

The within household secondary attack rate (SAR) is one such measure. It gives the proportion "attacked" (=infected) among individuals in contact with an infected case in a household during their entire period of infectiousness. From the model parameters the SAR for a carrier j and a susceptible i was derived

$$SAR_{ij} = P_{ij}(S \rightarrow C)_{d_j} = 1 - e^{-\beta_{ij} d_j} \qquad [6.6]$$

where d_j is the duration of carriage ($=1/\mu_j$, with j=c,a) and β_{ij} is the transmission rate from j to i. Applying the age-specific acquisition rates to formula [6.6], allows the estimates of SARs for the different age classes defined in the model. Moreover, the number of secondary infections in group i caused by a carrier in group j is derived as a function of the specific SARs and the household's composition, building a *next generation matrix* (NGM) (Diekmann & Heesterbeek, 2000) for each family size and structure

$$NGM_{ij}(z,a) = \begin{bmatrix} (z-a-1)\cdot SAR_{cc} & (z-a)\cdot SAR_{ca} \\ a \cdot SAR_{ac} & (a-1)\cdot SAR_{aa} \end{bmatrix} \qquad [6.7]$$

The dominant eigenvalues of each $NGM_{ij}(z,a)$ provide us with the average number of secondary infections produced by the introduction of one carrier in households with different sizes and structures (Basic Reproduction Number).

6.4.4 Prevalence of Pnc infection by household size and composition

A steady-state vector **v** of dimension 2^z was calculated from any of the family transition matrix (i.e. $\mathbf{T}_1(z,u)$) by solving the following system of equations

$$\mathbf{T}_1(z,u)\cdot \mathbf{v}(z,u) = \mathbf{v}(z,u) \qquad [6.8]$$

where **v** gives the proportion of households that are in each specific state at the equilibrium (Chin Long Chiang, 1980). From this the expected prevalence of infection in children and adults in a household of given size and structure can be calculated.

The proportion of community acquired Pnc infection was calculated using the steady-state vector **v** and deriving the expected number of new infections produced exclusively by household transmission ($k=0$) and comparing it to the expected number of those acquired from the community ($\beta=0$).

6.4.5 Model extensions (Matlab Individual Family Model)

To gain flexibility in the modelling framework that has just been explained and also to allow the inclusion of additional available information (i.e. individual characteristics such as better age stratification and day care attendance, and serotyping information) the model was also programmed in Matlab (Matlab 6.5 @ The MathWorks).

A transition matrix, as the one presented in equation 6.3, was built for each family (rather than for each group of families of the same size and composition). The family transition probabilities were generated taking into account the individual characteristics of the family members and, in particular, age (0-1, 2-4, 5-17 and 18+ years) and number of hours attending day-care (DC) per week. Though other important information was contained in the dataset (smoking status, antibiotics prescription, socio-economic indicators, etc.) it was decided to only consider, for the purpose of this work, the effects of the two most important individual risk factors for pneumococcal carriage (age, day-care attendance) (Givon-Lavi *et al.*, 1999;Principi *et al.*, 1999;Raymond *et al.*, 2000;Leino *et al.*, 2001;Neto *et al.*, 2003;Huang *et al.*, 2004). Moreover, the more flexible modelling framework that was developed allowed furthering the analysis and estimating serotype-specific pneumococcal transmission parameter. More on this will be said in Chapter 7.

Recovery rates (and thus duration of carriage) were estimated for the following age groups: 0-1, 2-4, 5-17 and 18+ years. The effect of day care attendance was explored modifying the community acquisition rate k - which was constant in the Excel model in each of the two age groups (section 6.4.5) - to take into account day care attendance among children <5 years of age:

$$K_g = k_g + k_{hr} \cdot hr \qquad [6.9]$$

where k_g represents the baseline community acquisition rate for children in the age group g (0-1, 2-4 years), k_{hr} is the acquisition rate per hour in the day care per week and hr is the number of hours per week spent in the day care.

6.5 Model results

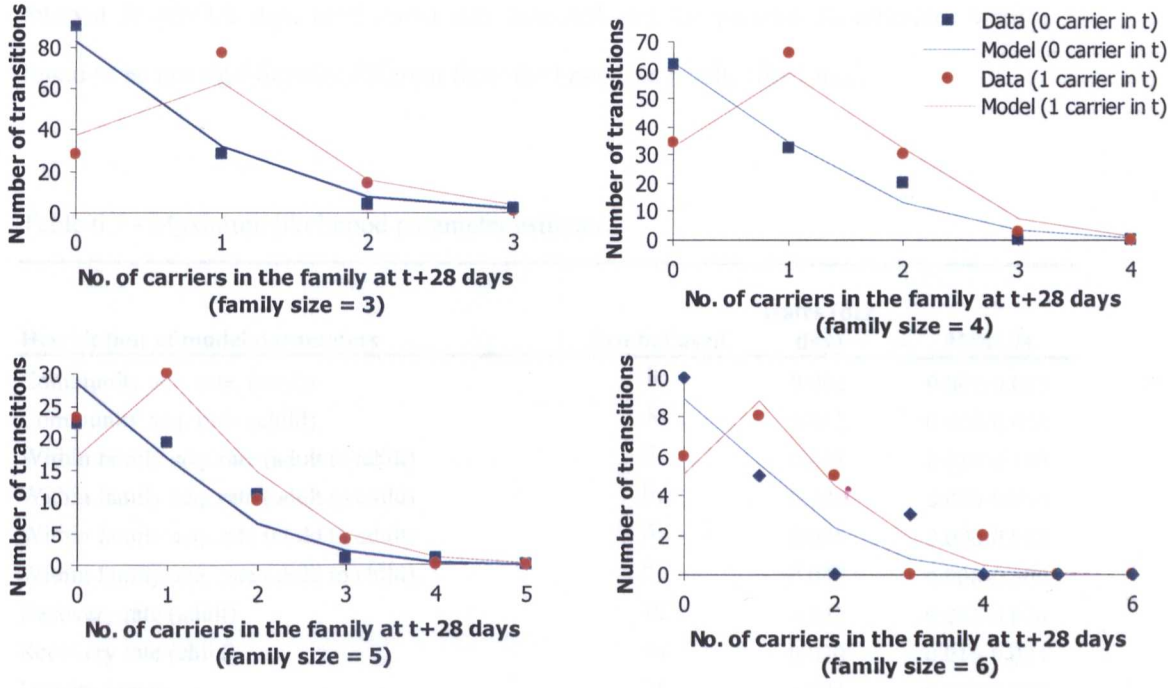
6.5.1 Excel model

In total 560 (51%) complete family transitions were available in the data (Table 6.6), the majority of which were found in family size of 3 and 4. The overall deviance obtained comparing the model log likelihood to the saturated log likelihood is 645, with 180 degrees of freedom (189 non-zero data points and 9 parameters to estimate). In Figure 6.4 the fit of the model is shown comparing the expected number of transitions estimated by the model, for uninfected families and families with one carrier, to the number observed from the data for the same transitions. The Chi-square tests of the model fit (not shown) did not show evidence of any significant difference between the model and the data.

Table 6.6 Number of complete transitions by family size and number of adults.

	Number of adults					
Family Size	**1**	**2**	**3**	**4**	**5**	**Total**
3	8	226	-	-	-	234
4	-	146	54	-	-	200
5	-	8	27	45		80
6	-	-	14	1	31	46
Total	8	380	95	46	31	560

Figure 6.4 – Model fit.



Transition probabilities obtained from the model for completely susceptible families (blue line) and families with one carrier (red line), compared to proportions of transition observed from carriage data (blue and red marks respectively).

Estimates of the 9 model parameters are shown in Table 6.7. In children less than 5 years of age the mean duration of pneumococcal carriage, derived using the inverse of the estimated recovery rate, is 51 days (95%CI: 42-64). The estimated mean duration of carriage in older family members is close to 19 days (95%CI: 14-24). The community acquisition rate for children (0.012 per day) is more than three times higher than that for adults (0.004 per day), showing that children <5 years of age are the most likely to

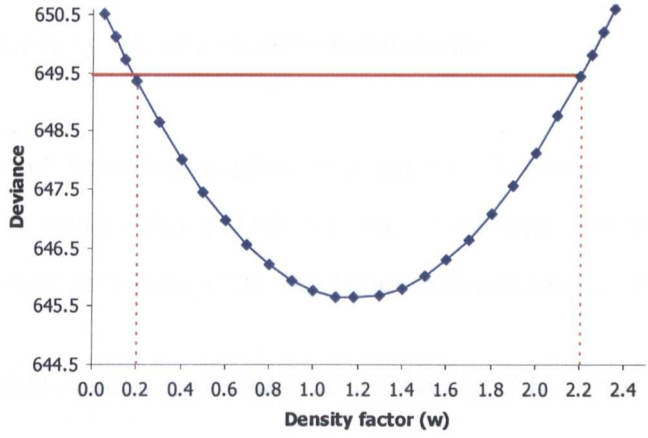
introduce the infection into the household. On the other hand, estimates of the within family acquisition rates show that the highest daily transmission rate is that from adults to children, whereas the lowest is the one from children to adults. These results are consistent with adults being more infectious but less susceptible to infection. A density coefficient significantly greater than zero (w=1.2; 95%CI: 0.2-2.2) is estimated from the model and suggests the importance of considering density dependent transmission. However, due to the very wide confidence interval, no clear indication is given on the strength of this effect (Figure 6.5). The sensitivity of the model to variation in the time interval δt (δt=1/2 day, δt=2 days) was assessed and the parameters estimates were found to be not significantly different from the base case results (δt=1 day).

Table 6.7 - Maximum likelihood parameter estimates

Description of model parameters	Symbol used	Rates (per day)	95%CIs
Community acq. rate (adult)	k_2	0.004	0.002-0.005
Community acq. rate (child)	k_1	0.012	0.008-0.016
Within family acq. rate (adult to adult)	β_{22}	0.048	0.010-0.180
Within family acq. rate (adult to child)	β_{12}	0.106	0.020-0.450
Within family acq. rate (child to adult)	β_{21}	0.005	0.000-0.018
Within family acq. rate (child to child)	β_{11}	0.047	0.008-0.200
Recovery rate (adult)	μ_2	0.053	0.041-0.070
Recovery rate (child)	μ_1	0.020	0.016-0.024
Density factor	w	1.184	0.200-2.200

Moreover, when looking at SAR measures that account for duration of infectiousness, the proportion of children infected by a child or adult is considerably higher (SAR_{cc}=0.40 and SAR_{ca}=0.32) than the proportion of adults infected by a child or adult (SAR_{ac}=0.09 and SAR_{aa}=0.16).

Figure 6.5 - Profile likelihood for the density factor (w).



The dotted lines are the 95% CI

In Table 6.8 estimates of the Reproduction Number are shown for the different family sizes and composition. R increases with the number of children present in the family. When 62% or over of the family members are aged less than 5 years, then the Reproduction Number reaches its threshold level (R=1). When at least 2 children are in the family, increasing the number of adults reduces R. This is the result of assuming w=1; i.e. the number of contacts remains the same in families of different sizes and, thus, the probability of getting in contact with other children in the family is smaller.

Table 6.8 Estimates of the Basic Reproduction Number for different household compositions

Number of children	No. Adults				
	1	2	3	4	5
1	0.407	0.529	0.583	0.613	0.632
2	0.773	0.716	0.689	0.677	0.672
3	1.033	0.910	0.834	0.785	0.753
4	1.203	1.062	0.964	0.895	0.845
5	1.320	1.176	1.071	0.992	0.932

Children: 0-5 years; adults: 5+ years; w is assumed to be equal to 1.

The expected prevalence of Pnc infection at equilibrium in both adults and children is given in Table 6.9. In order to have a baseline probability, the expected Pnc carriage in adults is estimated also for families with no children although no such families exist in

our data. The prevalence of Pnc carriage in adults does not vary much when bigger families are considered or when more children are present in the family. The expected prevalence in children increases with the number of children in the household. The prevalence increases by 3%-10% for each additional child.

The proportion of household acquired Pnc infection increases in bigger families, reaching 50% for both children and adults (Table 6.10). When only one child is in the family the proportion in children (22%-38%) is lower than in adults (34%-50%).

Table 6.9 Expected equilibrium prevalence of Pnc carriage in household with different compositions.

Prevalence	No. of children in the household	No. of adults in the household				
		1	2	3	4	5
Adults	0	0.06	0.10	0.11	0.12	0.12
	1	0.09	0.10	0.11	0.11	0.12
	2	0.10	0.11	0.11	0.11	-
	3	0.10	0.11	0.11	-	-
Children	1	0.44	0.47	0.48	0.49	0.50
	2	0.54	0.53	0.52	0.52	-
	3	0.58	0.56	0.55	-	-

Children: 0-5 years; adults: 5+ years; w is assumed to be equal to 1.

Table 6.10 Estimated proportion of within-family acquisition by household size and composition.

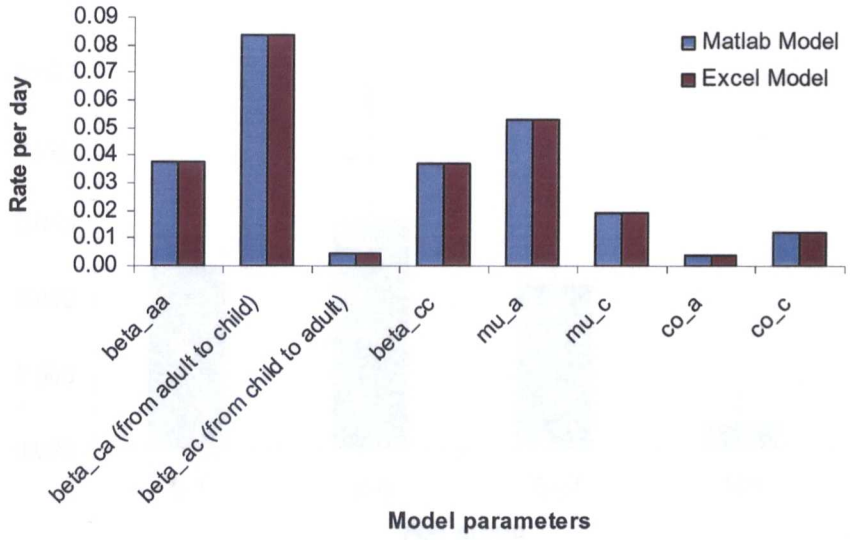
	No. of children in the household	No. of adults in the household				
		1	2	3	4	5
Adult	0	0%	40%	47%	50%	52%
	1	34%	41%	45%	48%	50%
	2	40%	42%	45%	47%	-
	3	42%	43%	45%	-	-
Child	1	22%	29%	33%	36%	38%
	2	46%	43%	43%	43%	-
	3	54%	50%	49%	-	-

Children: 0-5 years; adults: 5+ years; w is assumed to be equal to 1.

6.5.2 Matlab model

After checks were made to assess whether the Matlab model was producing the same results as the Excel model initially developed (Figure 6.6), parameter estimates were derived for the following age-groups: 0-1, 2-4, 5-17 and 18+ years.

Figure 6.6 – Comparison of Matlab and Excel models results.



Families of size 3 to 6 included and density factor equal to 1.

Figure 6.7 and Figure 6.8 show, respectively, the estimated age specific community acquisition rates and duration of carriage derived from the extended version of the model. Confirming the findings of the previous section, community acquisition rates are much lower in adults (18+ years of age) than among younger individuals. In particular children 2-4 years of age experience the highest rates being probably highly susceptible and exposed to pneumococci. Moreover, as shown in similar studies (Gray *et al.*, 1980;Ekdahl *et al.*, 1997;Auranen *et al.*, 2000), the duration of carriage decreases with age, with infants 0-1 years of age carrying pneumococci on average for 72 days (95%CI: 51-105) as opposed to older individuals, 2-4, 5-17 and 18+ age groups, who carry the organism for, respectively, 28, 18 and 17 days. These results will inform the modelling work of Chapter 8.

Figure 6.7 – Community acquisition rate by age and 95% CI (Matlab model).

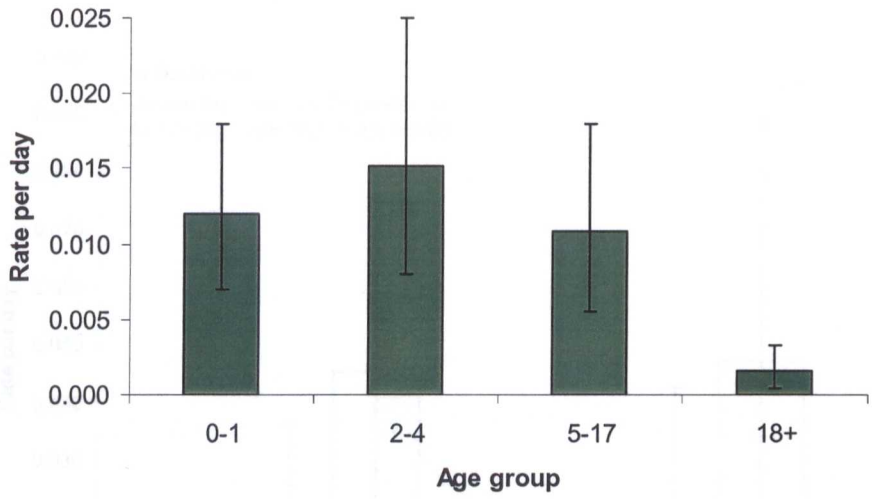
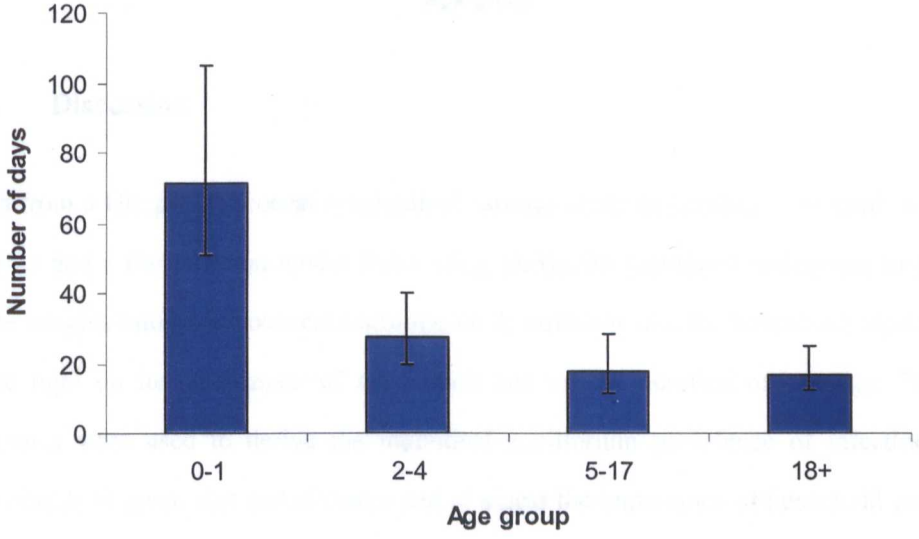
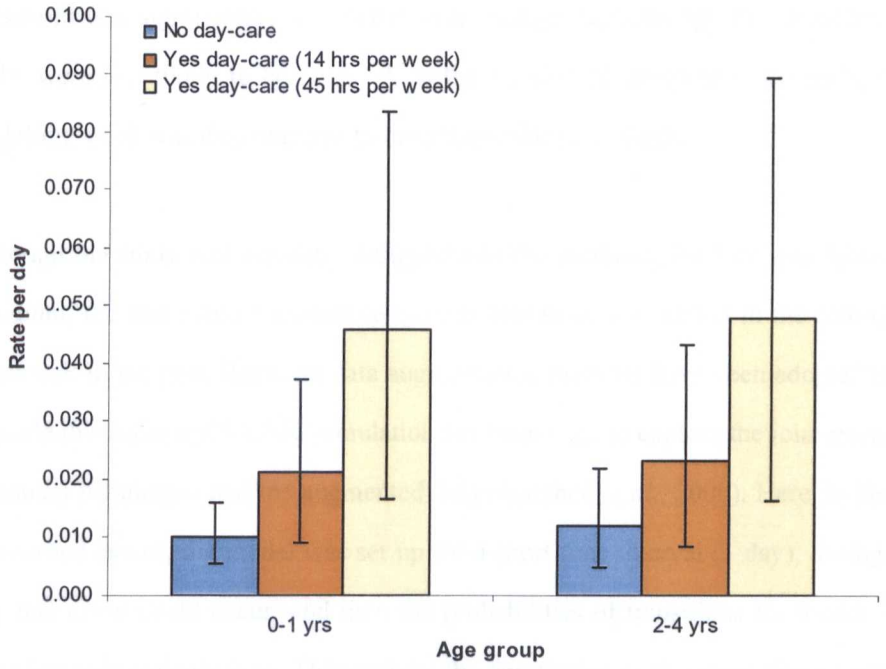


Figure 6.8 – Duration of carriage by age and 95%CI (Matlab model).



The importance of day care attendance is shown in Figure 6.9, where the estimated community acquisition rates in children <5 years of age are shown by age and day-care attendance (Yes DC attendance *vs.* No DC attendance). The average and the maximum number of hours attending the day-care per week and for the two age groups is used to estimate the overall community acquisition rates. These were respectively 14 and 45 hours per week.

Figure 6.9 – Community acquisition rates with 95%CI by age and day-care attendance (Matlab model).



6.6 Discussion

Data from a UK pneumococcal longitudinal carriage study in families were used in this chapter and a transmission model fitted using maximum likelihood techniques to gain some insights into pneumococcal transmission dynamics within the household, shedding some light on its mechanism of acquisition and on the duration of carriage. These estimates were used to derive the individual equilibrium prevalence of infection in households of given size and structure and to assess the importance of household *versus* community acquisition.

Interestingly, initial descriptive analysis of the dataset provided evidence of the absence of any seasonality in the carriage rates as opposed to invasive disease rates, which are much higher during the winter season (Chapter 3). This result, which is in contrast with previous finding (Lakshman *et al.*, 2003), suggest the importance of other factors (rather than colonisation rates) that may influence the disease pattern. These may include: the

circulation of other viruses in the population, climate changes, as well as the complex relationship between pneumococcal serotypes involved in carriage and/or causing disease. Moreover, the proportion of first introduction of a new serotype in the household was significantly associated with younger ages, though first introduction by adults were less likely to be detected, as their period of infection is generally shorter. Modelling work was thus required to investigate this issue further.

Although the study was carefully designed and the swabbing interval was forced to its minimum, the presence of unobserved events had to be considered in the setting up of the model. In the past, Bayesian data augmentation methods have been adopted in order to tackle this issue and MCMC simulation has been used to explore the joint posterior of the model parameters and the augmented data (Auranen *et al.*, 2000). Here, to deal with unobserved events, the model was set up for a short time interval (1 day), during which only one event could occur, and then the probabilities of transitions for longer (i.e. 28 days) intervals were derived. This enabled the description of the entire dataset with only nine model parameters.

The model classified individuals as 'carrier' or 'non-carrier' and it did not consider which serotype they were carrying. Acquisition and clearance rates were thus estimated for carriage of any serotype. Serotype-specific differences in acquisition and clearance rates were shown in the past (Smith *et al.*, 1993;Ekdahl *et al.*, 1997;Brueggemann *et al.*, 2003) and represent a very critical issue in terms of future disease burden and impact of vaccination policies. Here some baseline information on transmission dynamics were derived and, although the model allowed successive positive tests to be attributed to recovery and reacquisition, it did not exploit the information provided by a change of the serotype carried.

In agreement with previous findings, the model estimated that children carry the organism for longer periods than adult family members (72 *vs.* 17 days). Smith and colleagues (1993) estimated approximately two months of carriage in children for the

most common serotypes (6,19,23) and for Auranen and colleagues (2000) the mean duration of carriage for children aged under 2 years was 2.3 months (95%CIs: 1.5-3.3), which is extremely close to the estimate derived in this chapter (2.4 months). The estimated 1.5 months (95%CIs: 1.0-2.0) duration of carriage derived from the Finnish study (Auranen *et al.*, 2000) in 2 years of age and older is slightly higher than what was found here, though within the confidence interval that was derived for the 2-4 years of age. Slightly lower estimates of the duration of carriage were found in Ekdahl's study (Ekdahl *et al.*, 1997), where a significant relationship between carriage and age was estimated: 30, 21, 12, 15, 14 days for individuals aged, respectively, <1, 1-4, 5-6, 7-18 and 18+ years.

Estimates of pneumococcal acquisition rates from the community showed a difference between children and adults. The former were 3-4 times more likely to acquire the infection from the community and introduce the bacteria in their household's environment. Previous work by Auranen and colleagues (2000) showed a similar pattern although the difference between children and adults was stronger in the Finnish data and their rates were significantly lower than ours. This can probably be explained by the fact that their model considered only three serotypes that account for 30-60% of infections.

The within family transmission rates incorporate infectiousness of the carrier, susceptibility of the non-carrier and contact between them. Although various individual factors, such as age and immunity levels, may contribute to this relationship, the model used here is from the SIS class, and, thus, it does not explicitly account for immunity after infection. Nevertheless, transmission rates within the family were derived considering the age class to which both the carrier and the non-carrier belong, and suggested a higher level of susceptibility in children and infectiousness in adults.

The importance of density dependence when looking at transmission dynamics of infection has been discussed previously (McCallum *et al.*, 2001;Finkenstadt *et al.*, 2002). A density dependent factor was included in the analysis and found to be an

necessary element of the model to explain within-family transmission (w significantly greater than 0). However, at this stage, no clear judgement can be made on whether the transmission increases ($w<1$) or decreases ($w>1$) as a consequence of being in bigger families. More work could clarify this relationship and provide better estimates of within-family transmission that takes into consideration changes in the contact patterns in households of different sizes, environment and composition.

As expected, the prevalence of carriage for any family size and structure was higher for children than for adults. Moreover, whereas the prevalence in adults did not vary much for different family sizes and composition, the equilibrium prevalence in children increased with the number of children and adults in the family. This may again reflect the lower level of susceptibility in older individuals and the fact that they are less sensitive to changes in the proportion of infectious contacts they may have within the household.

Household-acquired infection made a major contribution to pneumococcal transmission in families both for children and adults. The more siblings were present in the family the more the infection could circulate among them and persist within the household. However, even in large families approximately 50%-60% of children and adults' infections were acquired outside the household.

The importance of age and day-care attendance as risk factors for pneumococcal carriage was further investigated developing a similar, but more flexible, model framework in Matlab. From this model, age-specific estimates of the community acquisition rates and duration of carriage confirmed our previous finding, though a better definition of the age strata was achieved with this version of the model. Age was associated with both community acquisition rates and duration of carriage, with higher levels among younger individuals. Moreover, day-care attendance was a risk factor for pneumococcal carriage. Community acquisition rate of children attending day-care centres were twice as high as the ones that did not attend day-care.

Longitudinal data can be quite challenging to analyse and many critical aspects have to be taken into account in doing so. Nevertheless they can provide a great contribution to the understanding of a pathogen's dynamics within the human host and on the way individual properties can affect transmission dynamics of the infectious agent. In this chapter some conclusions have been drawn about pneumococcal transmission dynamics, the contribution of community *versus* family transmission and the importance of family structure when considering the prevalence of infection within the household. In the following chapter further analysis will be provided which will focus on serotype specific carriage. Potential links between serotypes and transmission in the pre-vaccination era will be explored.

CHAPTER 7 - MODELLING SEROTYPE-SPECIFIC PNEUMOCOCCAL TRANSMISSION IN HOUSEHOLDS

7.1 Aims

- To expand the modelling framework developed in the previous chapter to include available data on serotype-specific pneumococcal carriage;
- To ascertain differences in within household acquisition rates as well as acquisition rates from the community for the most commonly carried serotypes (ST) (6B, 6A, 14, 23F, 19F);
- To estimate duration of carriage for the target ST and for different age groups;
- To investigate the existence of competition/interaction among the serotypes.

7.2 Introduction

In the previous chapter baseline estimates of transmission parameters have been derived using the available UK longitudinal dataset of carriage in households. These estimates, which are non serotype-specific, were derived using a modelling framework that enabled us to incorporate the two levels of clustering that are typical of any longitudinal dataset of individuals in households, schools, day-cares or any other social structure.

As seen in Chapter 3, however, *S.pneumoniae* is a very complicated and diverse organism, which is present worldwide in more than 90 distinctive serotypes. Though

only less than half of these appear to be circulating in the UK (Chapter 3) and some of those circulating are not causing disease (Chapter 6), the dissimilarities of the remaining types should be taken into account when investigating transmission dynamics.

This chapter aims to expand the previous modelling framework to enable potential differences among the carried serotypes to be assessed from the serotype-specific information that was available for the study population. As it was unfeasible to deal with all the carried types distinctively, the five most prevalent types (6A, 6B, 14, 19F, 23F) were investigated. The Matlab model (section 6.4.5) was used here and extended.

7.3 Method

7.3.1 Data

The longitudinal dataset on pneumococcal carriage in UK families, described in the previous chapter (section 6.3), was used in this analysis. Differently from the data used in Chapter 6, serotyping information, which was available for the study participants when carriage was detected, was included in this chapter. An example of the data is given in Figure 7.1 for a family of 4 individuals (2 adults and 2 children).

Figure 7.1- Example of carriage data for a family of 4 members.

Family code	Indiv code	Age	Swab 1	Swab 2	Swab 3	Swab 4	Swab 5	Swab 6	Swab 7	Swab 8	Swab 9	Swab 10
306	306RMC	18+ yrs										
306	306SAC	18+ yrs	6A									
306	306ERC	2 yrs	6B		6A		6B				19F	
306	306MGC	1 yr	6A	6B	6A	6A	19F	19F	6A	6A	19F	

Black cell=missing value; white cell=non carrier

Preliminary descriptive analyses on the serotypes being carried by the study participants were performed. The number of serotypes carried by each individual throughout the study period was extracted as well as the overall number of carriage episodes per carrier and per serotype carried. Moreover, the number of consecutive carriage episodes for the

most prevalent types was also derived and differences among the serotypes were highlighted.

The Matlab programme that was described in Chapter 6 (section 6.4.5) and that was used to improve the age stratification and to start exploring potential risk factors for pneumococcal carriage was further developed to investigate serotype-specific differences in both transmissibility and duration of carriage. The details of this analysis are given below.

7.3.2 Model structure

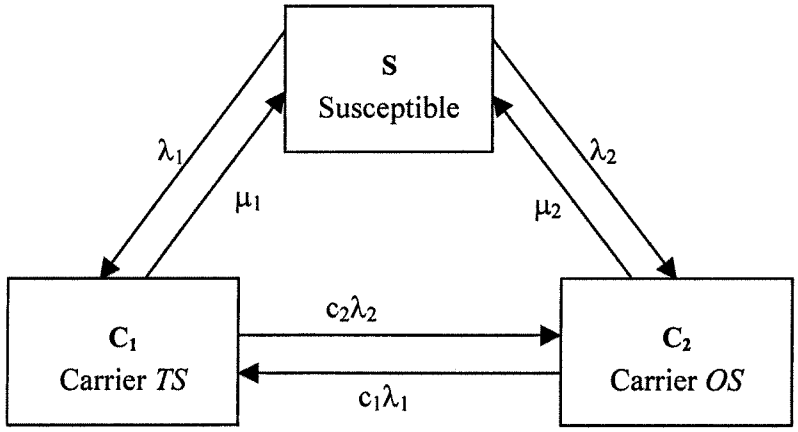
Using a similar structure to the one developed for the 2-state model, where the individual's state at each visit was coded as 0=susceptible and 1=pnc carrier, a 3-state model was built where individuals can be susceptible (status code = 0), carrier of one of the Target Serotypes *TS* (where *TS*: 6B, 6A, 14, 19F, 23F) (status code = 1) or carrier of any Other Serotype *OS* (status code = 2). In other words, due to the presence of 34 different serotypes in the dataset it was not possible to treat each of them separately and thus the model's framework was set to look at one serotype per time *vs.* carriage of any of the other 33 types. The household state at each visit was derived combining the carriage status of all the family members and resulted in a sequence of 0s, 1s and 2s if their information was complete. For example, the 9 possible statuses of a family of two individuals would be: 00, 01, 02, 10, 11, 12, 20, 21 and 22 (i.e.12 means that the first individual in the family was carrying the target serotype TS at a specific test point and the second person in the family was carrying one of the other 33 types). Five distinctive datasets were thus derived, i.e. one for each of the TS considered. For example, in Figure 7.1 the family status at the first swab is 0121 if TS=6A and 0212 if TS=6B.

As in Chapter 6 the individual probability of acquiring pneumococcus was defined as a function of two components: a within family acquisition rate and the acquisition rate from the community. Whereas community acquisition rates were age and serotype-

specific (but constant in time and in different households), the within family acquisition rate was time dependent being a function of the number of other household members carrying that particular type at that time.

An SIS structure was assumed (Figure 7.2), and thus no immunity after a carriage episode was considered in the current model. Thus, when individuals recovered from a carriage episode (at an age and serotype-dependent rate μ) they became susceptible again to that specific type as well as to other types. Moreover, a new type can be acquired although the host is already colonised by a different pnc serotype (C_1->C_2 and C_2->C_1). The force of infection (FOI), however, for both these flows is adjusted by two competition parameters (c_s, where s=1,2) that provide the relative risks of acquiring a serotype if already colonised with the other, compared with a noncarrier. When c_s=0, the model assumes complete competition between the types, so that the presence of one type fully protects against colonisation with the other types. When c_s=1 carriage of one type does not affect the individual susceptibility to other types. Moreover, the model assumed that individuals are co-colonised with more than one Pnc serotype for a very short period, after which one type will out-compete the other. This allowed the model structure to remain relatively simple (3 possible states to deal with) and close to our original model. The addition of a fourth state (co-colonised individuals, i.e. C_{12}) would have required the use of alternative statistical techniques due to the impossibility of dealing with 4 states within this modelling framework.

Figure 7.2 - SIS model structure for estimating serotype-specific transmission parameters.



TS=target serotype; OS=other serotypes

Due to the additional complication that generated from dealing with a 3-state (rather than 2-state) model, it was decided to adopt the simpler age stratification (<5, 5+ years) rather than the 4 age groupings that were used in section 6.4.5. The probabilities of transition from an infected to an uninfected state (C_s->S) and vice versa (S->C_s) in a short time interval δt were thus defined for an individual in the age class i=a,c (where c=child (<5 years) and a=adult (5+ years)). Differently from the previous model, these probabilities now also depend on the serotype *s* (where *s*=1,2).

The following set of equations describes the model probabilities of transition between the states:

$$P_i\,(C_s \rightarrow S)_{\delta t} = \mu_i^s \cdot \delta t \qquad [7.1]$$

$$P_i\,(S \rightarrow C_s)_{\delta t} = \lambda_i^s \cdot \delta t \qquad [7.2]$$

$$P_i\,(C_2 \rightarrow C_1)_{\delta t} = c_1 \cdot \lambda_{1i} \cdot \delta t \qquad [7.3]$$

$$P_i\,(C_1 \rightarrow C_2)_{\delta t} = c_2 \cdot \lambda_{2i} \cdot \delta t \qquad [7.4]$$

The FOI of type *s* for an individual in the age group i (+-5 yrs) is defined as follows:

$$\lambda_i^s = \left(k_i^s + \frac{\beta_{ia}^s I_a^s(t) + \beta_{ic}^s I_c^s(t)}{(z-1)^w} \right) \cdot \delta t \qquad [7.5]$$

where μ_i^s and k_i^s are, respectively, the clearance and the community acquisition rates of type *s* for age class i and z is the family size. $I_a^s(t)$ and $I_c^s(t)$ are the number of, respectively, infected adults and infected children (type *s*) in the family. β_{ij}^s is the transmission rate of type *s* from an infected to an uninfected individual and it reflects both the infectiousness of an individual in the age class j and the susceptibility of an individual in the age class i. It was assumed w=1, given that the estimate derived in the previous chapter was very close to one (w=1.184). A more detailed description of the model parameters can be found in Chapter 6 and is summarised in Table 7.1.

Table 7.1– Description of model parameters/variables and symbols.

Description of model parameters/variables	**Symbol used**
Community acquisition rate (child)	k_c^s
Community acquisition rate (adult)	k_a^s
Within family acquisition rate (adult to adult)	β_{aa}^s
Within family acquisition rate (adult to child)	β_{ca}^s
Within family acquisition rate (child to adult)	β_{ac}^s
Within family acquisition rate (child to child)	β_{cc}^s
Recovery rate (child)	μ_c^s
Recovery rate (adult)	μ_a^s
Density factor	w
Family size	z
Number of children in the HH carrying s at time t	$I_c^s(t)$
Number of adults in the HH carrying s at time t	$I_a^s(t)$
Relative risk of acquiring type 1 if already colonised with type 2	c_1
Relative risk of acquiring type 2 if already colonised with type 1	c_2

HH = household; s = 1,2

Different levels of model complexity (Table 7.2) were investigated comparing the overall likelihood and calculating the change in the deviance and in the number of parameters (d.f.). The following nested model structures were considered:

- *Model A0 (Baseline model)*: different community acquisition rates ($k_i^1 \neq k_i^2$)
- *Model A1*: different community acquisition rates and recovery rates, i.e different duration of carriage ($k_i^1 \neq k_i^2$ and $\mu_i^1 \neq \mu_i^2$)
- *Model A2*: different transmissibility ($\beta_{ij}^1 = \alpha\beta_{ij}^2$), community acquisition rates and recovery rates ($k_i^1 \neq k_i^2$ and $\mu_i^1 \neq \mu_i^2$)
- *Model A3*: different transmissibility ($\beta_{ij}^1 \neq \beta_{ij}^2$, 8 β_{ij} in the model), community acquisition rates and recovery rates ($k_i^1 \neq k_i^2$ and $\mu_i^1 \neq \mu_i^2$)

Model A1 was compared to model A0 and, if it resulted significantly different, A2 was compared to A1 and so on. When no statistically significant difference was detected the model was no longer considered.

Table 7.2 – Description of the parameters of the four model structures

	Model parameters			
Model	ST-specific β ($B^1 \neq B^2$)	ST-specific μ ($\mu^1 \neq \mu^2$)	ST-specific k ($k^1 \neq k^2$)	Number of parameters
A0	No	No	Yes	10
A1	No	Yes	Yes	12
A2	α factor	Yes	Yes	13
A3	Yes	Yes	Yes	16

B^s=beta matrices; μ^s=recovery rate vectors; k^s=community acquisition rate vectors, where $s=1,2$

Initially individuals already colonised by one type were assumed to be fully protected against carriage of other types ($c_1=c_2=0$). This assumption was then relaxed extending the best-fit model for each of the serotypes to incorporate competition between the TS and any other type (*Model B*).

7.3.3 Parameter estimation

Maximum likelihood techniques were used as in Chapter 6 to estimate the model parameters. Profile likelihood confidence intervals for predicted values were also calculated numerically (Armitage & Colton, 2004).

7.4 Results

7.4.1 Data

The maximum number of serotypes carried throughout the study period and among all study participants was 5. Two hundred and twenty two individuals (45%) carried 1 or 2 serotypes, 35 carried 3 (7%), and 20 (4%) carried 4 or 5 serotypes. In Figure 7.3 the proportion of individuals carrying 0,1-2, 3 or 4+ serotypes is shown for different age groups and highlights that children from 6 months to 4 years of age are the ones that carried the maximum number of serotypes during the 10-month period.

Some serotypes (6B, 19F, 23F, 6A, 14) were detected 6 or more times in the same individual though the majority of the types were found less than 3 times in the same person (Figure 7.4).

Figure 7.3 – Number of serotypes carried by each individual throughout the 10 months.

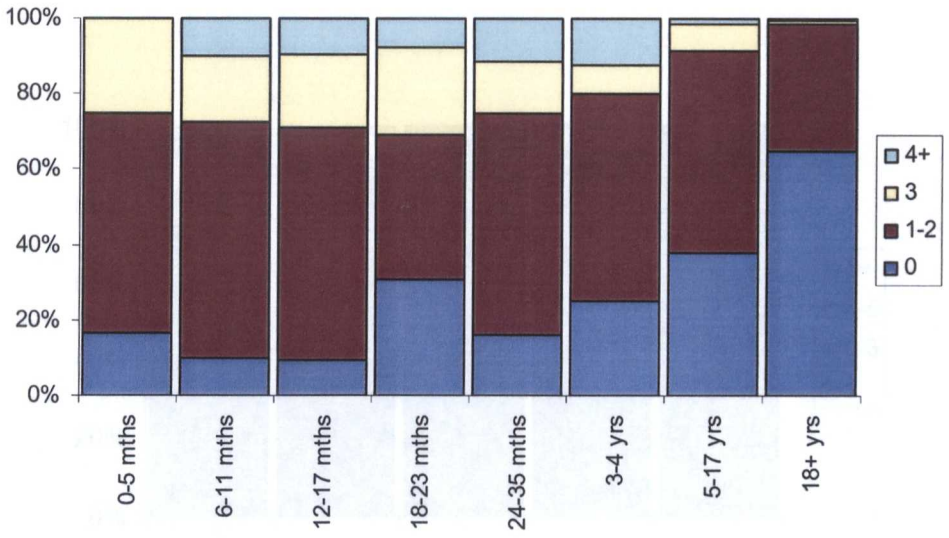
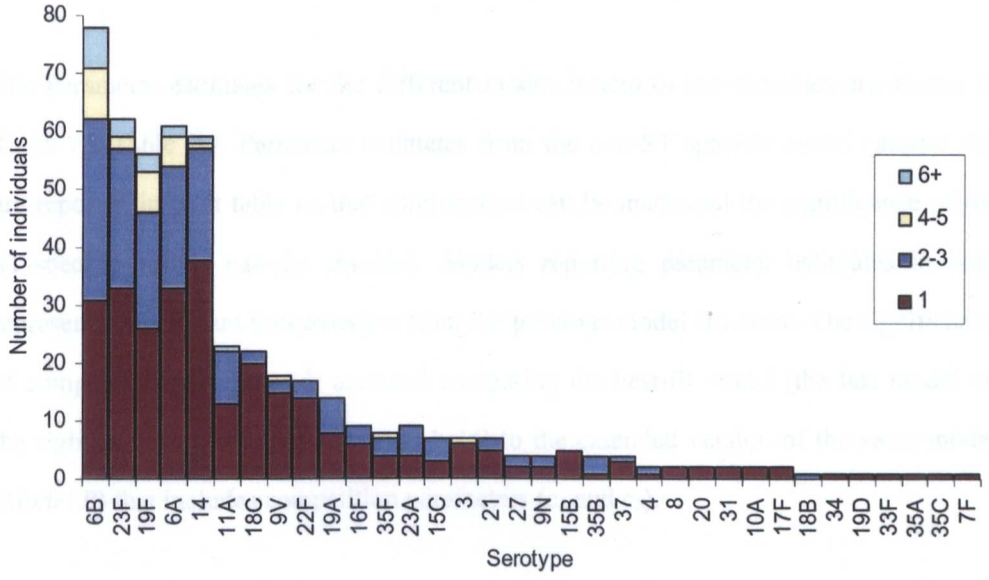
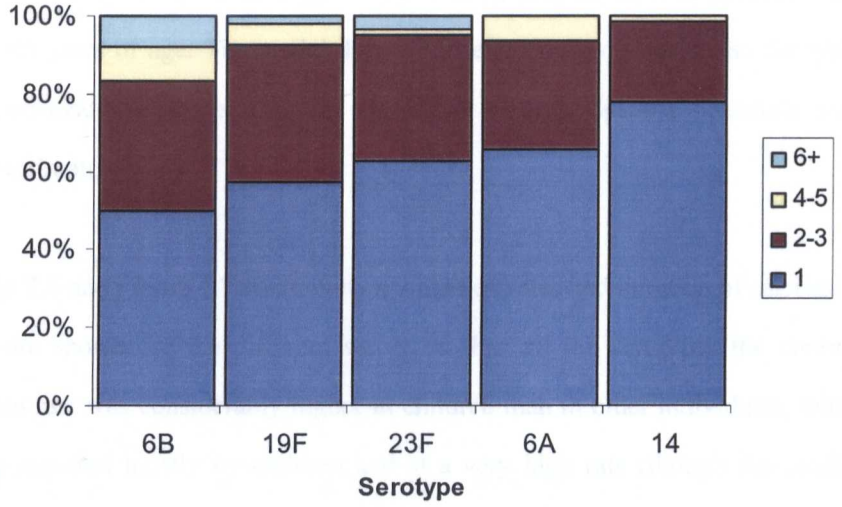


Figure 7.4 – Number of carriage episode per carrier per serotype.



In Figure 7.5 the proportions of consecutive carriage episode for the five most common types are given and show that serotypes 6B, 19F and 23F were found in 6 or more consecutive swabs, respectively, 8%, 2% and 3% of the times they were carried.

Figure 7.5– Number of consecutive positive swabs for the most prevalent serotypes.



7.4.2 Model results

The parameter estimates for the different model structures and p-values are shown in Table 7.3-Table 7.7. Parameter estimates from the non-ST specific model (*Model A0*) are reported in each table so that comparisons can be made and the significance of the ST-specific results can be assessed. Models reporting parameter estimates in bold represent a significant improvement from the previous model structure. The significance of competition parameters is assessed comparing the best-fit model (the last model on the right in each table with results in bold) to the extended version of the same model (*Model B*) that includes competition parameters (c_1 and c_2).

Evidence of a significant improvement in the model fit was demonstrated when comparing the non-ST specific model results to any of the ST-specific models. Estimates of the recovery rates (and thus duration of carriage) for serotype 6B were significantly different from the ones of the other types ($\chi_2^2=10$, $p<0.001$), with type 6B being carried on average 67 days in children < 5 years of age and only 9 days in older family members. Interestingly, serotype 6A appeared more transmissible than the other types

(α=4.85), after adjusting for differences in the recovery rate (χ_1^2=16, p=0.0011). For serotype 14 significant serotype and age-related differences in transmissibility and duration of carriage were detected (χ_3^2=16, p=0.001), with the latter as short as 7 days in children <5 years of age. The model derived different recovery rates also for type 19F whereas no evidence of a statistically significant serotype-specific behaviour for type 23F was estimated.

In Figure 7.6 and Figure 7.7 community acquisition rates and duration of carriage (with 95%CI) are shown for the different serotypes. For all the serotypes the community acquisition rate was considerably higher in children than in older individuals, with type 14 being acquired mostly by children and at a very high rate (though the confidence intervals are very wide). Differences in the duration of carriage were found both between the two age categories and also among the model serotypes. Results for types 6B, 6A and 23F confirmed the previous finding (Chapter 6) that the duration of carriage is longer at younger ages. On the other hand, the serotype specific model highlighted that for some of the types (i.e. 14 and 19F) this relationship may not be valid.

Table 7.3 – Model result (Target Serotype=6B).

Model parameters (TS=target serotype)	ST-specific model (TS= 6B)				
	Model A0	**Model A1**	Model A2	Model A3	**Model B**
beta_aa	0.041	**0.040**	0.041	0.042	**0.0345**
beta_ca (from adult to child)	0.111	**0.118**	0.122	0.117	**0.1117**
beta_ac (from child to adult)	0.003	**0.004**	0.005	0.007	**0.0051**
beta_cc	0.050	**0.048**	0.056	0.044	**0.0332**
beta_aa (TS)				0.013	
beta_ca (from adult to child) (TS)				0.072	
beta_ac (from child to adult) (TS)				0.001	
beta_cc (TS)				0.052	
mu_a	0.056	**0.051**	0.052	0.053	**0.0495**
mu_c	0.022	**0.025**	0.026	0.025	**0.0221**
mu_a (TS)		**0.117**	0.100	0.085	**0.2104**
mu_c (TS)		**0.015**	0.014	0.015	**0.0091**
co_a	0.004	**0.003**	0.003	0.003	**0.003**
co_c	0.009	**0.010**	0.010	0.010	**0.0089**
co_a (TS)	0.000	**0.001**	0.001	0.001	**0.0013**
co_c (TS)	0.003	**0.003**	0.003	0.003	**0.0012**
alpha			0.631		
c1					**100%**
c2					**33%**
MLL	1006.30	**1001.20**	1001.70	999.46	**989.41**
Duration of carriage					
Adult	18	**20**	19	19	**20**
Children	45	**39**	39	39	**45**
Adult (TS)		**9**	10	12	**5**
Children (TS)		**67**	70	67	**110**
Number of parameters	10	**12**	13	16	**14**
Change in the number of parameters		**2**	1	4	**2**
Change in the deviance		**10.2**	1.0	3.48	**23.58**
p-value		**0.006**	0.317	0.4809	**0.000**
Comparison model		**A0**	A1	A1	**A1**

Assuming w=1.

Table 7.4 – Model result (Target Serotype=6A).

Model parameters (TS=target serotype)	ST-specific model (TS= 6A)				
	Model A0	Model A1	**Model A2**	Model A3	**Model B**
beta_aa	0.044	0.043	**0.035**	0.037	**0.0306**
beta_ca (from adult to child)	0.122	0.121	**0.078**	0.098	**0.0670**
beta_ac (from child to adult)	0.004	0.004	**0.003**	0.000	**0.0026**
beta_cc	0.049	0.048	**0.035**	0.032	**0.0254**
beta_aa (TS)				0.140	
beta_ca (from adult to child) (TS)				0.219	
beta_ac (from child to adult) (TS)				0.026	
beta_cc (TS)				0.219	
mu_a	0.056	0.054	**0.050**	0.050	**0.0496**
mu_c	0.024	0.023	**0.021**	0.022	**0.0180**
mu_a (TS)		0.066	**0.120**	0.125	**0.1040**
mu_c (TS)		0.029	**0.035**	0.035	**0.0240**
co_a	0.003	0.003	**0.003**	0.003	**0.0031**
co_c	0.011	0.011	**0.011**	0.011	**0.0104**
co_a (TS)	0.000	0.001	**0.001**	0.000	**0.0006**
co_c (TS)	0.002	0.003	**0.003**	0.003	**0.0012**
alpha			**4.852**		**3.7397**
c1					**100%**
c2					**62%**
MLL	999.87	999.07	**991.87**	990.58	**983.03**
Duration of carriage					
Adult	18	18	**20**	20	**20**
Children	41	44	**47**	46	**55**
Adult (TS)		15	**8**	8	**10**
Children (TS)		35	**28**	28	**42**
Number of parameters	10	12	**13**	16	**15**
Change in the number of parameters		2	**3**	3	**2**
Change in the deviance		1.6	**16.0**	2.58	**17.68**
p-value		0.4493	**0.0011**	0.4610	**0.0001**
Comparison model		A0	**A0**	A2	**A2**

Assuming w=1.

Table 7.5 – Model result (Target Serotype=14).

Model parameters (TS=target serotype)	ST-specific model (TS= 14)				
	Model A0	**Model A1**	**Model A2**	**Model A3**	**Model B**
beta_aa	0.047	**0.048**	**0.036**	**0.055**	**0.0446**
beta_ca (from adult to child)	0.118	**0.132**	**0.103**	**0.099**	**0.0770**
beta_ac (from child to adult)	0.008	**0.008**	**0.006**	**0.002**	**0.0027**
beta_cc	0.047	**0.046**	**0.042**	**0.041**	**0.0306**
beta_aa (TS)				**0.000**	**0.0067**
beta_ca (from adult to child) (TS)				**0.771**	**0.2036**
beta_ac (from child to adult) (TS)				**0.038**	**0.0352**
beta_cc (TS)				**0.234**	**0.0657**
mu_a	0.058	**0.063**	**0.057**	**0.060**	**0.0575**
mu_c	0.025	**0.021**	**0.020**	**0.020**	**0.0174**
mu_a (TS)		**0.044**	**0.066**	**0.047**	**0.0481**
mu_c (TS)		**0.067**	**0.094**	**0.134**	**0.0564**
co_a	0.003	**0.003**	**0.003**	**0.003**	**0.0031**
co_c	0.012	**0.011**	**0.011**	**0.011**	**0.0100**
co_a (TS)	0.000	**0.000**	**0.000**	**0.000**	**0.0001**
co_c (TS)	0.002	**0.004**	**0.005**	**0.006**	**0.0029**
alpha			**3.389**		
c1					**60%**
c2					**100%**
MLL	991.71	**981.30**	**976.85**	**968.73**	**962.30**
Duration of carriage					
Adult	17	**16**	**18**	**17**	**17**
Children	40	**48**	**50**	**50**	**58**
Adult (TS)		**23**	**15**	**21**	**21**
Children (TS)		**15**	**11**	**7**	**18**
Number of parameters	10	**12**	**13**	**16**	**18**
Change in the number of parameters		**2**	**1**	**3**	**2**
Change in the deviance		**20.82**	**8.9**	**16.24**	**12.86**
p-value		**0.0000**	**0.0029**	**0.0010**	**0.0016**
Comparison model		**A0**	**A1**	**A2**	**A3**

Assuming w=1.

Table 7.6 Model result (Target Serotype=19F).

Model parameters (TS=target serotype)	ST-specific model (TS= 19F)				
	Model A0	**Model A1**	Model A2	Model A3	**Model B**
beta_aa	0.042	**0.042**	0.043	0.055	**0.0365**
beta_ca (from adult to child)	0.101	**0.102**	0.104	0.098	**0.0855**
beta_ac (from child to adult)	0.005	**0.004**	0.005	0.003	**0.0041**
beta_cc	0.040	**0.040**	0.040	0.037	**0.0325**
beta_aa (TS)				0.014	
beta_ca (from adult to child) (TS)				0.161	
beta_ac (from child to adult) (TS)				0.006	
beta_cc (TS)				0.047	
mu_a	0.056	**0.061**	0.062	0.065	**0.0613**
mu_c	0.022	**0.020**	0.020	0.019	**0.0187**
mu_a (TS)		**0.029**	0.028	0.025	**0.0231**
mu_c (TS)		**0.030**	0.030	0.032	**0.0194**
co_a	0.003	**0.003**	0.003	0.004	**0.0035**
co_c	0.011	**0.010**	0.010	0.010	**0.0087**
co_a (TS)	0.000	**0.000**	0.000	0.000	**0.0003**
co_c (TS)	0.002	**0.003**	0.003	0.003	**0.0024**
alpha			0.879		
c1					**13%**
c2					**73%**
MLL	985.07	**981.30**	981.25	979.13	**975.18**
Duration of carriage					
Adult	18	**16**	16	15	**16**
Children	46	**51**	51	51	**54**
Adult (TS)		**34**	35	40	**43**
Children (TS)		**33**	33	31	**52**
Number of parameters	10	**12**	13	16	**14**
Change in the number of parameters		**2**	1	4	**2**
Change in the deviance		**7.54**	0.1	4.34	**12.24**
p-value		**0.0231**	0.7518	0.3619	**0.0022**
Comparison model		**A0**	A1	A1	**A1**

Assuming w=1.

Table 7.7 Model result (Target Serotype=23F)

Model parameters (TS=target serotype)	ST-specific model (TS= 23F)				
	Model A0	Model A1	Model A2	Model A3	**Model B**
beta_aa	0.040	0.040	0.037	0.037	**0.032**
beta_ca (from adult to child)	0.096	0.095	0.090	0.107	**0.070**
beta_ac (from child to adult)	0.006	0.006	0.005	0.002	**0.005**
beta_cc	0.041	0.042	0.038	0.045	**0.031**
beta_aa (TS)				0.055	
beta_ca (from adult to child) (TS)				0.035	
beta_ac (from child to adult) (TS)				0.013	
beta_cc (TS)				0.033	
mu_a	0.054	0.055	0.054	0.053	**0.053**
mu_c	0.023	0.021	0.021	0.021	**0.019**
mu_a (TS)		0.050	0.054	0.061	
mu_c (TS)		0.032	0.034	0.031	
co_a	0.003	0.003	0.003	0.003	**0.003**
co_c	0.012	0.011	0.011	0.011	**0.009**
co_a (TS)	0.000	0.000	0.000	0.000	**0.000**
co_c (TS)	0.003	0.003	0.003	0.003	**0.002**
alpha			1.390		
c1					**15%**
c2					**76%**
MLL	1001.50	999.64	999.27	997.51	**989.83**
Duration of carriage					
Adult	18	18	19	19	**19**
Children	43	47	48	47	**54**
Adult (TS)		20	19	17	
Children (TS)		31	30	32	
Number of parameters	10	12	13	16	**12**
Change in the number of parameters		2	3	6	**2**
Change in the deviance		3.72	4.5	7.98	**23.34**
p-value		0.1557	0.2159	0.2396	**0.000**
Model comparison		A0	A0	A0	**A0**

Assuming w=1.

Figure 7.6- Community acquisition rate from ST-model A3, 8 betas.

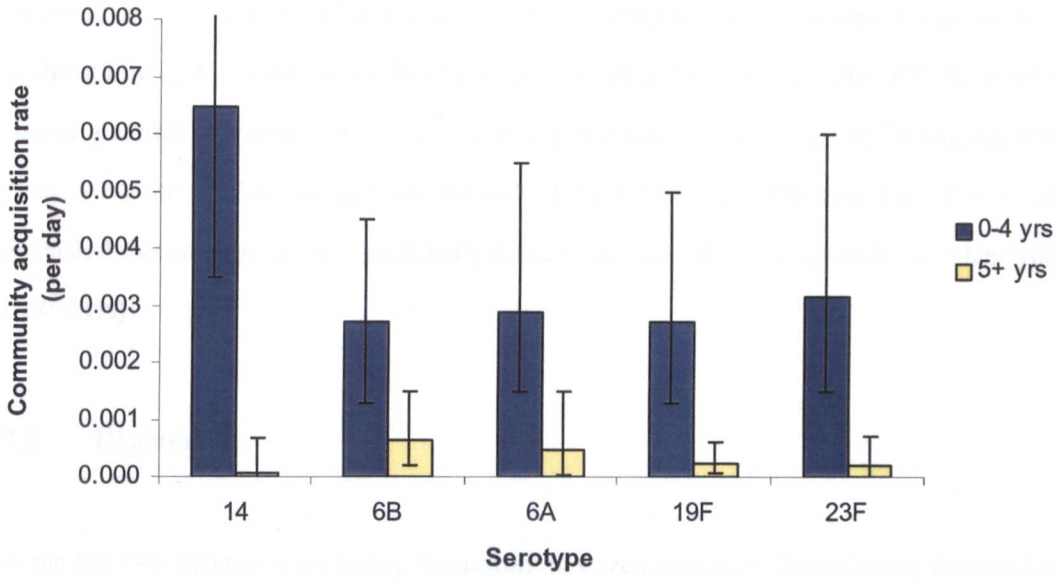
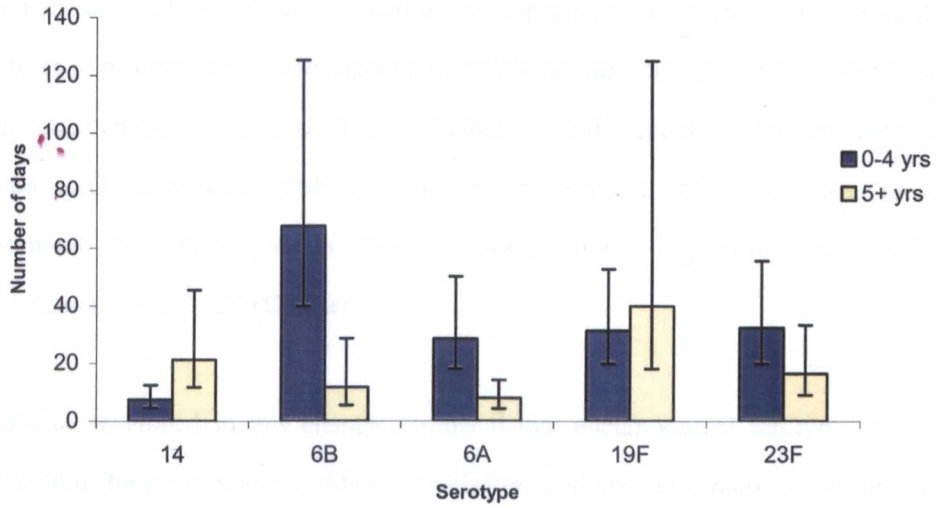


Figure 7.7- Duration of carriage from ST-model A3, 8 betas.



In the tables above the relative risks of acquiring the TS if already colonised by the other serotype are given in *Model B* for the different serotype and using the best-fit model. It was

assumed that c_1 may be different to c_2, which implies that the reduction in the FOI of the target serotype (when the individual is carrying some other type) is not equal to the one observed in the other types when the individual is carrying the target serotype. Large variation in the ability of TS to colonise individuals carrying other types were shown with the relative risk of a carrier of another ST (compared with a non-carrier) acquiring the TS ranging from 60%-100% for ST 6A, 6B and 14, but only 13%-15% for ST 19F and 23F. The model estimated that carriage of 6B significantly reduces the individual susceptibility to other types (RR=33%).

7.5 Discussion

In the last two chapters a modelling framework has been presented for analysing longitudinal family carriage studies. The model developed in Chapter 6 was here extended in order to incorporate serotype-specific information at the individual level that was produced during the study period when carriage was detected. This was an essential extension considering that evidence of the diversity of *S.pneumoniae* serotypes had already been shown in the past (Smith *et al.*, 1993;Ekdahl *et al.*, 1997;Brueggemann *et al.*, 2003). To ignore these dissimilarities would have been inappropriate, especially considering that one of the final objectives of this thesis is to investigate pneumococcal transmission dynamics in the presence of an intervention strategy such as vaccination. Differences in the characteristics of pneumococcal serotypes as well as strain interaction (competition) may lead to serotype replacement after the implementation of a vaccination policy (Lipsitch, 1997;Lipsitch, 1999;Lipsitch *et al.*, 2000) (Chapter 8).

The model developed in this chapter estimated that pneumococcal serotypes may present substantial differences in terms of both colonisation and clearance rates. Some serotypes (6A and 14) appeared to be more transmissible and with higher clearance rates than the other types, with children carrying serotype 6A for longer than adults and the other way around for serotype 14. The duration of carriage for serotype 6B was considerably higher in children (67

days) than in adults (9 days) as well as for serotype 23F, though, for the latter, the difference was not as striking (31 *vs.* 20 days) and not statistically significant (p-value >0.1).

Interestingly, the overall community acquisition rate, obtained adding the 5 serotype-specific rates derived here, is considerably higher than the one estimated for all the serotypes together in the non serotype-specific model of Chapter 6 (0.018 vs. 0.012). This highlights the major limitation of the non serotype-specific model, which consisted in not using the serotype information and assuming that prolonged carriage episode occurred rather than clearance and acquisition of a different serotype.

Allowing for partial competition between the serotypes (i.e individuals can be infected with one serotype when already colonised by a different one) improved the model fit substantially. Estimates of the competition parameters showed that carriage of some serotypes (i.e. 6B) might significantly reduce the individual susceptibility to other types. Moreover, the relative risk of a carrier (compared with a non-carrier) acquiring serotypes 6A, 6B and 14 was quite high (69-100%) as opposed to the one for ST 19F and 23F, which was around 15%.

Great dissimilarities have been estimated between the five target serotypes, both in terms of transmission parameters and of existing interactions that may influence their behaviours. These represent important aspects in the analysis of host-pathogen interactions. Modelling work on interference among viruses was addressed by the pioneering works of Dietz (Dietz, 1979) and Elveback and colleagues (1964;1968) who looked at competition of two virus populations in a community and derived mathematical conditions for coexistence. Their work has been greatly extended in recent years (Dietz, 1979;May & Nowak, 1994;Nowak & May, 1994;Gupta *et al.*, 1994a;Gupta *et al.*, 1994b;Gomes *et al.*, 2002) when several models for multi strain infections have started to appear in the literature addressing issues such as intraspecific competition, replacement, cross immunity between strains and super-infection, in which one strain replaces another within the host. Gupta and colleagues (1994a), in particular, introduced the concept of parasite heterogeneity in the mathematical modelling field, and

showed the effects of intraspecific parasite diversity (i.e. virulence and transmissibility) on the transmission dynamics of *Plasmodium falciparum*.

To our knowledge, this is the first time that the level of competition/interaction between different variants of the same organism in human population has been estimated. Lipsitch and colleagues (2000) investigated competition among two pneumococcal serotypes in a mouse model and found that carriage of the resident strain (6B) significantly inhibited acquisition of the challenge strain (23F) at the lowest challenge dose. However, the inhibition did not appear at higher doses of the challenge strain. The framework developed here has certainly taken forward the understanding of pneumococcal transmission dynamics that was achieved in the previous chapter. This is a highly diverse pathogen, and to consider all the different variants that are circulating as if they were the same (as we did in Chapter 6) certainly represents a major limitation. However, the model developed here does suffer from one significant problem, which consist of being able to include only one serotype at a time. Ideally, a multiple serotype model should have been used to investigate the diversity among the serotypes and to establish a one-to-one relationship, at least, between the most common ones. An individual based model would be necessary to incorporate the dissimilarities we have found among the serotypes and the development of such a model is beyond the scope of this thesis.

The following chapter presents a transmission dynamic model of carriage of vaccine and non-vaccine serotypes. It was intended that the analysis presented here would inform the competition parameters in the model. Unfortunately, the complex relationship between the serotypes precludes a detailed parameterisation of this model. Nevertheless, the results presented here certainly suggest that competition between serotypes may well exist. Hence, serotype replacement must be considered in models of the effectiveness and cost-effectiveness of pneumococcal conjugate vaccine. These are addressed in the following chapters.

CHAPTER 8 - DYNAMIC MODELS OF PNEUMOCOCCAL CARRIAGE AND VACCINATION

8.1 Aims

- To develop and apply a transmission dynamic model to assess the effect of different vaccination strategies on the age-specific prevalence of carriage of vaccine (VT) and non-vaccine (NVT) serotypes.

8.2 Introduction

As reported in Chapter 2 of this thesis, evidence from various countries has started to build up over the past few years on the direct and indirect effects of conjugate vaccines against pneumococcal carriage and disease. Though most of the available literature highlights a reduction in both carriage and disease among vaccinated and unvaccinated individuals, some data are also available on an increase in the carriage prevalence of serotypes not contained in the vaccine. Moreover, an increase in disease caused by non-vaccine serotypes has been observed suggesting that replacement in carriage may also lead to replacement in disease (Chapter 2). This phenomenon may not only have worrying implications on the outcome of any vaccination programme but should also be considered when evaluating its economic acceptability and the consequent allocation of public health resources.

Mathematical models have been used extensively to describe the dynamics of infectious diseases (Anderson & May, 1991) and to predict the effects of vaccination against many childhood infections, including rubella, measles (Anderson & May, 1983;Babad *et al.*, 1995;Gay, 2004) and varicella (Halloran *et al.*, 1994;Brisson *et al.*, 2000). Through

modelling, the direct and indirect effects of intervention programmes (such as herd immunity, change in the age distribution of disease) have been investigated and policies have been implemented on their findings. The effects of intervention programmes on multi-strain bacteria, such as the pneumococcus, are, however, complex. Predicting them requires analysis of the interaction (or interference) between the circulating serogroups as well as knowledge of their characteristics, i.e. duration of carriage, transmissibility and pathogenicity/invasiveness.

The impact of vaccination on the coexistence of competing strains of the same pathogen was addressed firstly by McLean (McLean, 1995) and a few years later by White and colleagues (White LJ *et al.*, 1998). White and colleagues (1998) conceptualised different forms of interaction through the immunity developed by the hosts and noted that 'the disturbance of the observed equilibrium by vaccination against the observed strain can allow other, out-competed, strains to invade or increase in incidence/prevalence'. Over the past few years, a few attempts to model *S.pneumoniae* infection have started to appear in the literature (Lipsitch M., 1997;Lipsitch M., 1999;Auranen *et al.*, 2000;Temime *et al.*, 2003;Eerola *et al.*, 2003;Temime *et al.*, 2004) and, although complete information on the biological and immunological characteristics of the organism is still missing, some insights into its transmission pattern have started to build up. Lipsitch (1997) developed a deterministic transmission dynamic model to look at the impact of vaccination against *H.influenzae* and *S.pneumoniae*, both colonizing bacteria with multiple serotypes. This model differs from the previously developed models (May & Nowak, 1994;Nowak & May, 1994;McLean, 1995) as it assumes that hosts can be co-infected with multiple serotypes and that competition between serotypes is mediated by reduced colonization probabilities in a host already colonized with another serotype. Recently, the importance of these indirect effects on the dynamics of resistant pneumococci has been investigated by Temine and colleagues (2003;2004) who showed not only that an overall reduction of colonization may not occur (i.e. non-vaccine serotypes may replace vaccine ones) but also that vaccination alone may not be successful in controlling selection for resistance in *S.pneumoniae*.

In the previous two chapters novel modelling techniques have been utilised to estimate pneumococcal transmission parameters and duration of carriage episodes. The diversity of the organism has been highlighted and knowledge of the serotype-specific differences in transmissibility and duration of carriage has been taken forward. In this chapter a realistic age-structured (RAS) transmission dynamic model (Schenzle, 1984) will be developed to look at the medium and long-term effects of vaccination on carriage of vaccine and non-vaccine serotypes. Parameter estimates will be drawn, where possible, from Chapter 6 where pneumococcal carriage in general was looked at rather than serotype specific behaviours. Parameter estimates obtained in Chapter 7, though they have deepened the understanding of the diversity of pneumococci, will not be used here.

The three aspects that differentiate this model from previous works (Lipsitch, 1997;Lipsitch, 1999) are: the inclusion of a realistic age structure, the use of parameters estimated from population-based carriage data and the mixing assumptions. An age-structured model was considered essential to assess the public health and economic impact of different vaccination policies, since the risk of disease (IPD, pneumonia, otitis media) is highly correlated with age (Chapter 3). Moreover, age-related vaccination programmes (such as addition of booster doses, or age-based campaigns) are under consideration and to properly evaluate their impact, the age-specific prevalence of VT and NVT post-vaccination needs to be derived. In the past, transmission dynamic models of *S.pneumoniae* have all assumed homogenous mixing (i.e. random mixing), which means that every individual is equally likely to come into contact with every other individual regardless of age, sex, or other stratification. This is not a reasonable assumption for pneumococcal disease, where transmissibility (and thus the force of infection) is not age independent (Chapter 6). Alternative forms of mixing pattern will be explored here and their impact on the outcome of the different vaccination strategies (in terms of the overall and age-specific prevalence of carriage) will be assessed.

It is important to note that the analysis of this Chapter (which only considers pneumococcal carriage), represents the first step in the investigation on the impact of vaccination programmes and further work will be pursued to extend the current model to include

pneumococcal disease (IPD, pneumonia, otitis media). This should provide estimates of the changes from pre to post-vaccination in the disease incidence rates for England and Wales, which could then be used to improve the economic evaluations presented in Chapter 9.

This chapter is structured as follows. Firstly, a section on the estimation of the force of infection for VT and NVT from the longitudinal carriage dataset presented in Chapter 6 will be provided. This is necessary information to parameterise any mathematical model of pneumococcal carriage and transmission. Secondly the development of a RAS transmission dynamic model for pneumococcal VT and NVT carriage will be presented. In the results section the impact of different vaccination strategies will be investigated and sensitivity analyses of the different model assumptions will be performed. A discussion section will conclude the chapter.

8.3 Estimating the force of infection

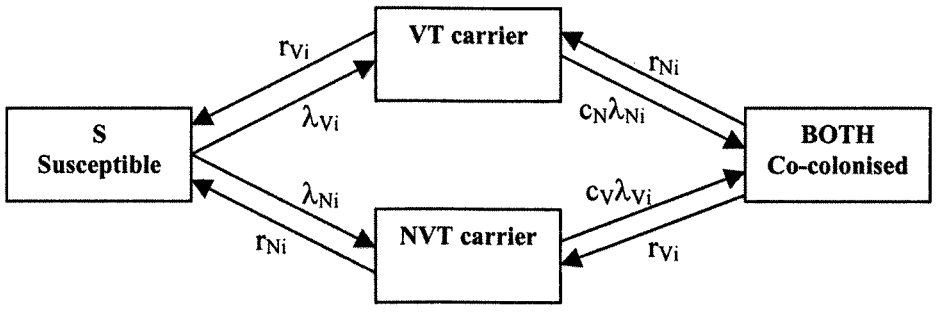
As seen in Chapter 2, a number of factors may influence the individual propensity to carry an organism such as the pneumococcus. From individual characteristics (such as age, health status, etc) to other external factors related to the condition of the environment in which the person is. Whereas more complicated modelling techniques are needed in order to factor in the latter elements, individual characteristics, such as age, can be included in relatively simple deterministic models by adopting age-dependent parameters. The force of infection, defined as the 'per-capita rate at which susceptibles acquire infection' (Anderson & May, 1991) is, for many pathogens, age-dependent, and is a function of the probability of effective contacts between individuals, which may vary by age, and the age-dependent prevalence of infection. Whereas the latter can be inferred from population based study, such as the longitudinal study presented in Chapter 6, effective contact rates are much more difficult to estimate as they depend on a number of factors difficult to measure, most importantly individual susceptibility and infectiousness, and type of contacts. Estimating the force of infection is a crucial step for any transmission dynamic model as it provides ways of estimating the effective contact rates, which otherwise would be unknown.

8.3.1 Method

8.3.1.1 Model definition

The first stage in parameterising the force of infection is to choose an appropriate model structure. As the analysis in Chapter 6 showed, individuals are likely to experience many episodes of pneumococcal carriage in a lifetime, so a strict SIR model would be inappropriate. The simplest structure is an SIS model. Alternatively, models including temporary or partial immunity could be used (Gomes *et al.*, 2004). Though models with immunity may be the most appropriate to consider pneumococcal carriage and transmission, it would require a complicated structure which could incorporate serotype specific immunity and also cross protection between serotypes (i.e. carriage of one serotype may not provide equal protection against all other serotypes), with a corresponding increase in the number of parameters required to be estimated. However, due to the fact that VT and NVT were considered here and that definitive information on the cross protection between serogroups is lacking, an SIS model structure, similar to the one used in Chapter 7, appears to be adequate. This model structure is the most parsimonious option, and will assist in further model development (Figure 8.1).

Figure 8.1 SIS model structure for estimating the forces of infection for VT and NVT



The model parameters are described in Table 8.1. Differently from the structure of Figure 7.2, individuals of age i can be co-colonised by one serotype that belongs to the VT group and another one that falls into the NVT category (i.e. 14 and 5). However, the rate at which co-colonisation occurs depends on the age-dependent force of infection (see later section) and

also on two *competition* parameters that determine the relative risk of acquiring a vaccine serotype if already colonised by a non-vaccine serotype (c_V) and vice versa (c_N). These parameters are similar to the ones that were used in Chapter 7 to regulate the flows VT->NVT and NVT->VT, although in the current chapter co-colonisation status is explicitly considered. As the knowledge on the interactions between vaccine and non-vaccine serotypes is scarce, the effects of three levels of competition are explored in the following analysis. These are c=0.1 (strong competition: carriers of one type are less likely to acquire the other type than individuals who are not carrying), c=0.7 (weak competition), c=1 (no competition: VT and NVT carriage prevalence are independent).

Table 8.1 – Description of model parameters/variables and symbols used.

Description of model parameters/variables	**Symbol used**
Age-dependent recovery rate from VT carriage	r_{Vi}
Age-dependent recovery rate from NVT carriage	r_{Ni}
Age-dependent force of infection of VT	λ_{Vi}
Age-dependent force of infection of NVT	λ_{Ni}
Relative risk of acquiring VT if already colonised by a NVT	c_V
Relative risk of acquiring NVT if already colonised by a VT	c_N

The subscript i represents the age group

8.3.1.2 Model parameters

The recovery rate was assumed to be equal to the inverse of the duration of carriage, estimated to be 72, 28, 18 and 17 days for, respectively the 0-1, 2-4, 5-17 and 18+ age groups (Chapter 6). Recovery rates for VT and NVT were assumed to be the same ($r_{Vi}=r_{Ni}$). Though this is a simplistic and, possibly, unrealistic assumption, the wide diversity of the serotypes in terms of recovery rates (Chapter 7) does not allow an accurate estimate of the recovery rate for vaccine and non-vaccine serotypes.

The forces of infection for, respectively, VT and NVT were assumed to be step functions, so that a constant value was assumed within each of the following age groups: 0-1, 2-4, 5-9, 10-19, 20-29, 30+ years.

8.3.1.3 Fitting the model to the data

Maximum likelihood (Brown & Rothery, 1993;Williams & Dye, 1994;Hilborn & Mangel, 1997) was used to fit the model and function parameters to the carriage data (see Chapter 6, section 6.4.1 for more details).

To fit the force of infection model parameters to the carriage data, where individuals can exist in one of the 3 mutually exclusive compartments (S, VT, NVT) a multinomial model was required. For simplicity, it was assumed that all co-colonised individuals were detected as vaccine-serotype carrier and, thus, included in the VT compartment. This appeared a reasonable assumption as the serotyping procedure in the laboratory favoured the detection of vaccine serotypes (personal observation). The log likelihood of this model is:

$$\log L = \sum_{i=1}^{n} [VT_i \cdot \log vt_i + NVT_i \cdot \log nvt_i + S_i \cdot \log s_i] + constant \qquad [8.1]$$

Where i = age group, VT = observed number of VT carriers, *vt*=predicted prevalence of VT carriers, NVT = observed number of NVT carriers, *nvt*=predicted prevalence of NVT carriers, S = observed number of susceptibles, *s*=predicted prevalence of susceptibles.

The saturated log likelihood (i.e. the log likelihood that would be expected if the model predicted the observed data perfectly) was derived and the deviance was calculated as twice the difference between the saturated log likelihood ($logL^*$) and the model log likelihood (logL): Deviance = $2*(logL^* - logL)$. The combination of parameter values that minimised the deviance were obtained using Excel's solver tool. The carriage data were split into 16 age groups, which gave 20 degrees of freedom (16*2-12 parameters).

8.3.2 Results

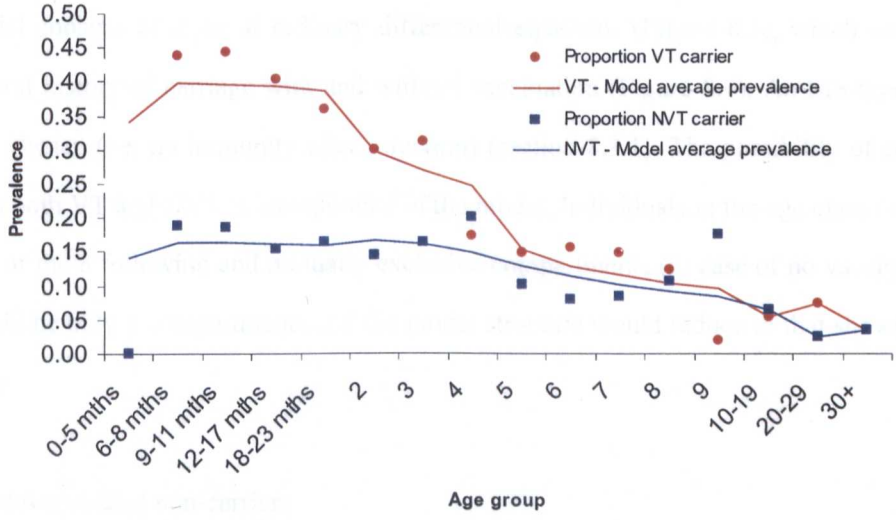
The best fitting force of infection parameters for the SIS model are shown in Table 8.2 and the resulting carriage prevalence curves are shown in Figure 8.2, where the model estimates are compared to the observed data. The model appeared to fit well, except at age 0-5 months. This results in a deviance of 37-39 (depending on which competition parameter was adopted)

which, given the 20 degrees of freedom, indicated that it remained a fairly small amount of unexplained variability in the data (p=0.006), mostly due to the lack of fit in the first five months of life (which contributed 16 to the overall deviance) (Figure 8.2). Although in fact 3 children aged 0-5 months (n=16) were found to be carriers, for none of them serotype information was available and thus these data were not included in the analysis.

Table 8.2 Estimated weekly force of infection for VT and NVT by age and competition parameters.

	c=0.1		c=0.7		c=1	
Age group	**VT**	**NVT**	**VT**	**NVT**	**VT**	**NVT**
0-1	0.1026	0.0438	0.0847	0.0438	0.0781	0.0439
2-4	0.0687	0.0418	0.0588	0.0415	0.0550	0.0415
5-9	0.0399	0.0355	0.0368	0.0354	0.0355	0.0354
10-19	0.0239	0.0295	0.0229	0.0294	0.0224	0.0295
20-29	0.0336	0.0107	0.0331	0.0107	0.0328	0.0107
30+	0.0152	0.0156	0.0151	0.0156	0.0149	0.0156
Deviance	**39.09**		**38.08**		**37.65**	

Figure 8.2 Estimated vs. observed carriage prevalence by age.



Best-fit force of infection parameters and strong competition (c=0.1).

The remaining part of this chapter will focus on the development of the transmission dynamic model using the forces of infection and the steady state prevalences just derived.

8.4 Transmission dynamic model

8.4.1 Method

8.4.1.1 Population

In the model, the population of England and Wales is assumed to be stable (i.e. births equal deaths) and no migration occurs. Individuals are born into age class 0 at the start of the year and live to the age of 75 years, at which point they die. Mortality is assumed to be zero up to this point. The model has a realistic age structure (Schenzle, 1984) and consists of 75 cohorts of individuals (0, 1, 2, 3,...74), which corresponds to each year of age. At the end of each year individuals grow older: a person in the age group *i* moves into age group *i+1* (3 years old become 4, etc.) and newly born infants enter the age group 0.

8.4.1.2 Model structure

A compartmental transmission dynamic model (Anderson & May, 1991) was developed to examine the influence of competition and vaccination on the equilibrium prevalence of serotypes contained and not contained in the 7-valent pneumococcal conjugate vaccine. The model consists of a set of ordinary differential equations (Figure 8.3), which describes the natural history of carriage with and without vaccination (Figure 8.4). An SIS-type of model was chosen (i.e. no immunity after infection) (section 8.3.1). The possibility of co-infection with both VT and NVT is incorporated in the model. Individuals in the age class *i* can exist in one of the 8 following and mutually exclusive compartments (in case of no vaccination there would be only 4 compartments and the model structure would reduce to that shown in Figure 8.1):

S = unvaccinated non-carriers

VT = unvaccinated Vaccine-Type carriers

NVT = unvaccinated Non-Vaccine-Type carriers

B = unvaccinated co-colonised individuals

Sv = vaccinated non-carriers

VTv = vaccinated Vaccine-Type carriers

NVTv = vaccinated Non-Vaccine-Type carriers

Bv = vaccinated co-colonised individuals

Individuals are born into the susceptible class at age 0 at the start of each year. Susceptible unvaccinated (S) and vaccinated (Sv) individuals become infected (VT or NVT) according to the age-specific force of infection of, respectively, vaccine-type (λ_{Vi}) and non-vaccine-type (λ_{Ni}) pneumococci. These forces of infection are allowed to vary according to the number of VT and NVT carriers that are present in the population and the age-specific contact rates β_{ij}, which will be described in the next section. Individuals carrying VT become co-colonised (B) according to the force of infection of NVT and the competition parameter (c_N) described earlier. The same goes for NVT carriers becoming also infected with VT at a rate $c_{VT}\lambda_{Vi}$. Individuals recover naturally from carriage (VT, NVT, B) at an age-dependent rate r_i (see section 8.3.1.2 and 8.4.1.4 for details).

Figure 8.3– Dynamic model structure in equations (see also figure 8.1)

$$\frac{dS_i(t)}{dt} = r_{Vi} \cdot VT_i(t) + r_{Ni} \cdot NVT_i(t) - S_i(t) \cdot (\lambda_{Vi}(t) + \lambda_{Ni}(t)) - \nu_i S_i(t) + \omega \cdot Sv_i(t)$$

$$\frac{dVT_i(t)}{dt} = S_i(t) \cdot \lambda_{Vi}(t) - c_N \cdot \lambda_{Ni}(t) \cdot VT_i(t) - r_{Vi} \cdot VT_i(t) + r_{Ni} \cdot B_i(t) - \nu_i VT_i(t) + \omega \cdot VTv_i(t)$$

$$\frac{dNVT_i(t)}{dt} = S_i(t) \cdot \lambda_{Ni}(t) - c_V \cdot \lambda_{Vi}(t) \cdot NVT_i(t) - r_{Ni} \cdot NVT_i(t) + r_{Vi} \cdot B_i(t) - \nu_i NVT_i(t) + \omega \cdot NVTv_i(t)$$

$$\frac{dB_i(t)}{dt} = c_N \cdot \lambda_{Ni}(t) \cdot VT_i(t) + c_V \cdot \lambda_{Vi}(t) \cdot NVT_i(t) - B_i(t) \cdot (r_{Ni} + r_{Vi}) - \nu_i B_i(t) + \omega \cdot Bv_i(t)$$

$$\frac{dSv_i(t)}{dt} = r_{Vi} \cdot VTv_i(t) + r_{Ni} \cdot NVTv_i(t) - Sv_i(t) \cdot ((1-\gamma) \cdot \lambda_{Vi}(t) + \lambda_{Ni}(t)) + \nu_i S_i(t) - \omega \cdot Sv_i(t)$$

$$\frac{dVTv_i(t)}{dt} = Sv_i(t) \cdot (1-\gamma) \cdot \lambda_{Vi}(t) - c_N \cdot \lambda_{Ni}(t) \cdot VTv_i(t) - r_{Vi} \cdot VTv_i(t) + r_{Ni} \cdot Bv_i(t) + \nu_i VT_i(t) - \omega \cdot VTv_i(t)$$

$$\frac{dNVTv_i(t)}{dt} = Sv_i(t) \cdot \lambda_{Ni}(t) - c_V \cdot \lambda_{Vi}(t) \cdot (1-\gamma) \cdot NVTv_i(t) - r_{Ni} \cdot NVTv_i(t) + r_{Vi} \cdot Bv_i(t) + \nu_i NVT_i(t) - \omega \cdot NVTv_i(t)$$

$$\frac{dBv_i(t)}{dt} = c_N \cdot \lambda_{Ni}(t) \cdot VTv_i(t) + c_V \cdot \lambda_{Vi}(t) \cdot (1-\gamma) \cdot NVTv_i(t) - Bv_i(t) \cdot (r_{Ni} + r_{Vi}) + \nu_i B_i(t) - \omega \cdot \dot{Bv}_i(t)$$

$$\lambda_{Vi} = \sum_j \beta_{Vij} \cdot (VT_j(t) + VTv_j(t) + B_j(t) + Bv_j(t))$$

$$\lambda_{Ni} = \sum_j \beta_{Nij} \cdot (NVT_j(t) + NVTv_j(t) + B_j(t) + Bv_j(t))$$

Where i is the age group, ν_i represents the vaccine coverage in age group i, r_v and r_n are, respectively, the recovery rates from VT and NVT infection, ω is the rate of waning of vaccine-induced protection, c_N and c_V represent the relative risk of acquiring, respectively, NVT and VT if already a carrier of the other type (i.e. competition parameters), γ is the vaccine efficacy against VT carriage, $\lambda_{Vi}(t)$ and $\lambda_{Ni}(t)$ represent the age-specific force of infection for, respectively, VT and NVT pneumococci at time t and β_{Vij} (β_{Nij}) is the effective contact rate for VT (NVT) between an infected individual in the age group j and a susceptible in the group i.

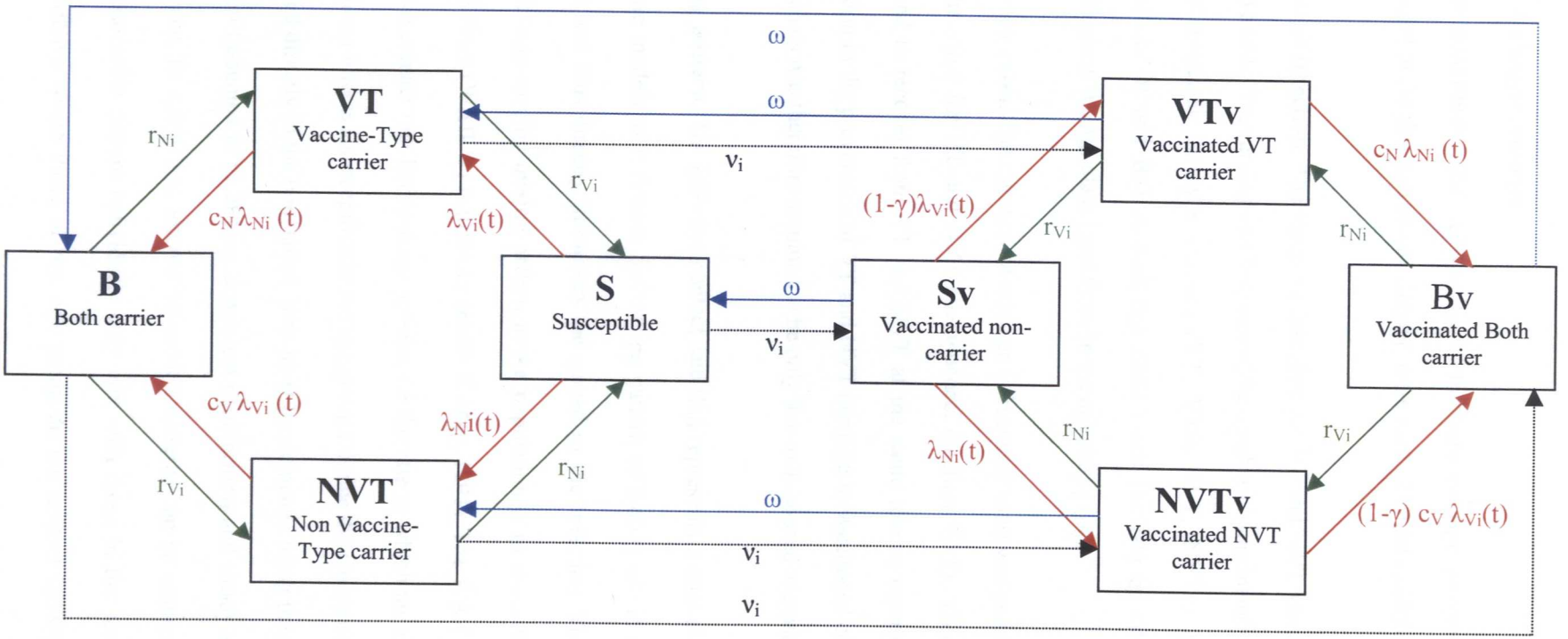
Vaccination occurs at one point in age, such that in a routine vaccination programme all infants are vaccinated at the same time, and in a catch-up campaign individuals in the targeted age group are immunised according to the planned vaccination schedule. This assumes that vaccination occurs as a discrete event at a specified time point, rather than at a constant rate. Following vaccination a proportion (=vaccine coverage) of individuals moves into the equivalent vaccinated compartment according to their status (S->Sv, VT->VTv, NVT-

>NVTv, B->Bv) and gain partial protection against VT carriage acquisition. The force of infection of VT pneumococci, among vaccinated individuals, is reduced by a factor (1-γ) where γ is the vaccine efficacy. The force of infection of NVT among vaccinated individuals remains the same as the one among unvaccinated individuals. Vaccinated individuals may lose their protection and go back to the equivalent 'unvaccinated' compartment (Sv->S, VTv->VT, etc.). This occurs at a waning rate w (=1/duration of protection) that is constant throughout all ages and all the compartments.

8.4.1.3 Model analysis

Numerical results were generated using ModelMaker version 4.0 software (ModelKinetix, Reading, UK). The system was solved using high order Runge-Kutta integration of ordinary differential equations with fixed time steps. The model simulated 20 years (five years pre-vaccination and 15 years after vaccination) and each run contained 1300 time steps (52 steps each year, i.e. weekly time steps). The effects of vaccination on both VT and NVT prevalence of carriage was explored.

Figure 8.4 – Dynamic model structure



Key

λ_{Ni} (t) and λ_{Vi} (t)=force of infection with non-vaccine (N) and vaccine (V) serotypes respectively in age group i
r_{Ni} and r_{Vi} = recovery rates for NVT and VT in age group i
γ = vaccine efficacy against VT carriage acquisition
ν_i = vaccine coverage in age group i
c_N and c_V = competition parameters
ω=waning rate of vaccine induced protection

8.4.1.4 Parameterisation

Initial conditions. The age-specific equilibrium carriage prevalences for VT and NVT, estimated in the first part of this chapter, were used as initial conditions for the model.

Forces of infection. The forces of infection for VT and NVT were age and time dependent ($\lambda_{Ni}(t)$ and $\lambda_{Vi}(t)$), varying as a function of the number of vaccinated and unvaccinated vaccine and non-vaccine serotype carriers (VT, VTv, NVT, NVTv) as well as co-colonised individuals (B and Bv) in each age class i and the rate of effective contacts between individuals in the age class i and those in the age class j (β_{ij}).

Recovery rates. The duration of carriage (1/recovery rate) was assumed to be age dependent and the same for VT and NVT pneumococci (section 8.3.1). Vaccinated individuals were assumed to recover from VT and NVT at the same rate as unvaccinated individuals. The reduction in the prevalence of VT and NVT carriage in vaccinated compared to unvaccinated individuals was therefore assumed to be only due to a reduced acquisition rate.

Mixing pattern. The effective contact rate (β_{ij}) represents a crucial element in transmission dynamic models as it defines the mixing pattern of individuals in different age or activity groups and thus directly influences the spread of the infection. The standard technique to consider age-specific mixing pattern in the population is to use a Who-Acquired-Infection-From-Whom (WAIFW) matrix (Anderson & May, 1991). The WAIFW matrix represents the effective contact rate between age groups, i.e the rate at which an infected individual in the age group j infects a susceptible in the age group i. Since the elements of the matrix cannot be observed directly in the population, they must be estimated using the pre-vaccination force of infection (assumed to be at time dependent equilibrium) and steady state values for carriage prevalence. In doing this, alternative mixing patterns can be explored, which can go from fully assortative (where individuals only mix with those in the same age group), to fully disassortative where those of one age group do not contact individuals of the same age.

Between these two extremes an infinite number of alternative mixing patterns are possible (Garnett & Anderson, 1993).

The effective contact rates (β_{Vij} and β_{Nij}) were calculated from the equilibrium values of λ_{Vi} and λ_{Ni} (section 8.3) and the number of VT and NVT carriers in the population at steady state (i.e. initial conditions) and for different values of the competition parameters (c=0.1, 0.7, 1). Intially, proportional mixing was assumed in order to derive the values for the β_{ij}. This type of mixing arises when individuals make contacts with other people in their own or other groups in proportion to the number of contacts that are supplied from each group (Garnett *et al.*, 1992)

$$\phi_{ij} = \frac{c_i c_j N_j}{C} \qquad [8.2]$$

where c_i and c_j are the number of contacts provided by each individual in, respectively, group i and j, N_j is the number of individuals in group j and C is the total number of contacts in the population.

Effective contact rates were also estimated assuming a fully assortative mixing pattern

$$\psi_{ij} = \begin{cases} 0 & \text{where } i \neq j \\ \dfrac{\lambda_i}{I_i} & \text{where } i = j \end{cases} \qquad [8.3]$$

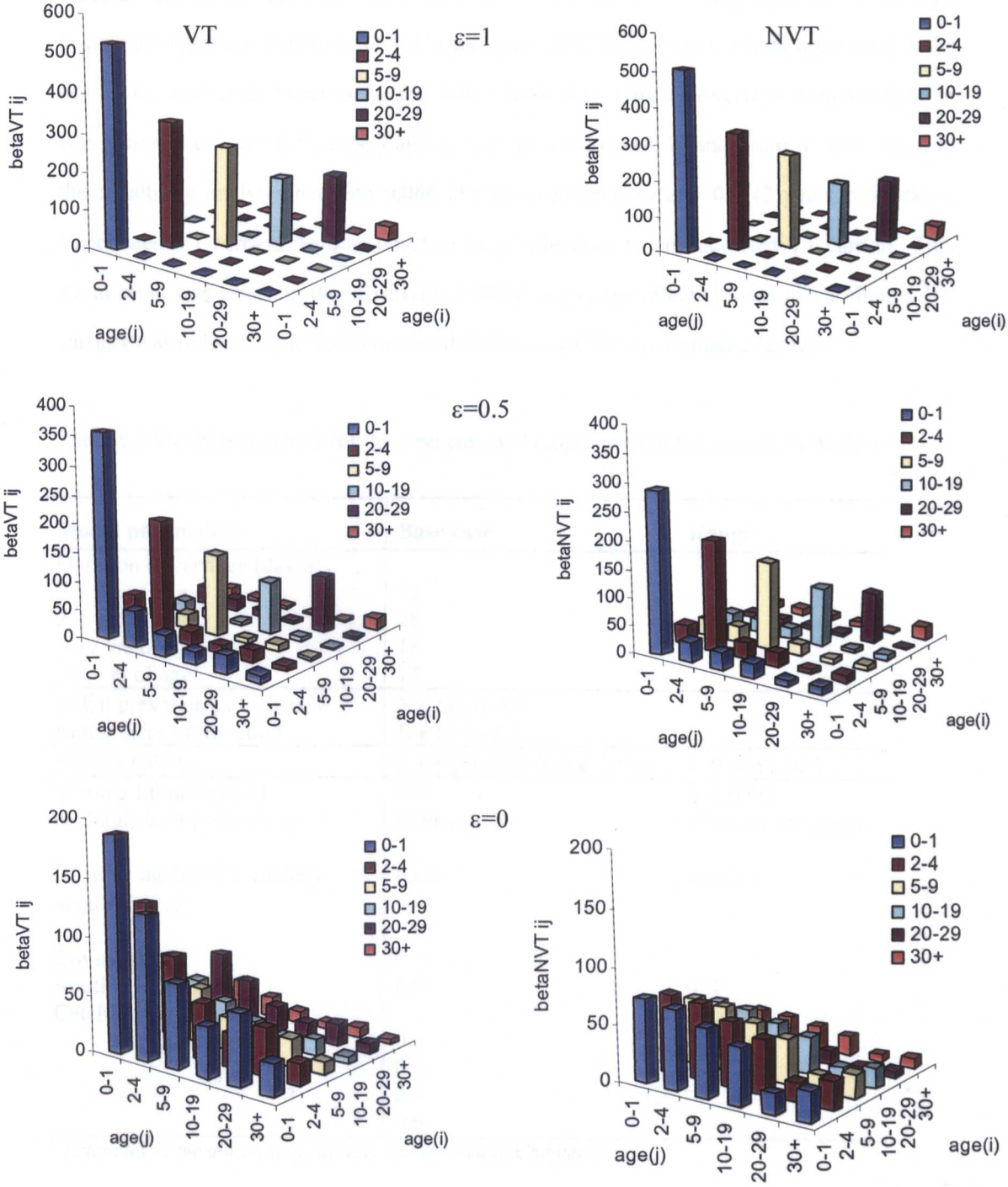
where I_i is the number of infected (carrier) individuals. This allowed exploring intermediate levels of mixing (i.e. in between a fully assortative and a proportionate mixing) using the following formula

$$\beta_{ij} = \varepsilon \cdot \psi_{ij} + (1 - \varepsilon) \cdot \phi_{ij} \qquad [8.4]$$

and ε denotes the degree of assortative mixing (Garnett & Anderson, 1993). When ε=1, mixing is entirely assortative and when ε=0 mixing is proportionate.

In Figure 8.5 the different estimates for the elements of the WAIFW matrices are shown, for both VT and NVT and assuming different levels of assortativeness ($\varepsilon=0,0.5,1$).

Figure 8.5 Values of β_{ij} for VT and NVT assuming a different mixing patterns and strong competition between serotypes (c=0.1)



The left (right) column corresponds to the effective contact rates for VT (NVT). Top graphs correspond to fully assortative mixing ($\varepsilon=1$), middle graphs to an intermediate level of mixing ($\varepsilon=0.5$) and the bottom graphs correspond to proportionate mixing ($\varepsilon=0$).

In the following analysis the proportionate mixing is chosen as the base case, as a fully assortative mixing assumption would appear unrealistic. The effect of having intermediate mixing patterns is, however, explored in the sensitivity analysis.

Vaccine associated parameters. In the base case, vaccine efficacy against VT carriage acquisition (γ) is assumed to be 68% (Dagan *et al.*, 2002) although this level was varied in the sensitivity analysis between 30% and 90% (Table 8.3). Direct protection from vaccination was assumed to last for 5 years (Lakshman *et al.*, 2003) (w=0.2) and again, w was varied in the sensitivity analysis between 0.066 (15 years protection) and 0.5 (2 years protection). Vaccinated VT carriers were assumed to be as infectious as unvaccinated VT carriers. This assumption was tested in the sensitivity analysis where the infectiousness of vaccinated VT carriers was reduced up to 70% compared to the one of VT unvaccinated carriers.

Table 8.3 Model parameters for the base case and ranges used in the sensitivity analyses.

Model parameters	**Base case**	**Range**
Duration of carriage (days)[a]:		
0-1 yrs of age	72	
2-4 yrs of age	28	
5-17 yrs of age	18	
18+ yrs of age	17	
Initial prevalence of carriage	*See figure 8.3*	
Initial force of infection	*See table 8.1*	
Mixing pattern	*See figure 8.4 (top graphs)*	ε=0 and ε=0.5
Waning immunity (w) (1/duration of protection)	0.2 (5 years)	0.5, 0.06 (2 years, 15 years)
Efficacy against VT carriage acquisition (γ)	0.68	0.3, 0.9
Coverage (v)		
Routine vaccination	0.6	0, 1
Catch-up vaccination		
Age (years): 1	0.6	
2	0.6	
3	0.6	
4	0.6	

[a] *Estimates of the duration of carriage are derived in Chapter 6*

8.4.1.5 Alternative vaccination policies

The alternative vaccination strategies investigated were:

- *Strategy 1*: routine vaccination at 3 months of age;
- *Strategy 2*: routine vaccination at 3 months of age, plus a catch-up campaign targeting all those under the age of 5;
- *Strategy 3*: routine vaccination at 1 year of age;
- *Strategy 4*: routine vaccination at 1 year of age, plus a catch-up campaign targeting all those under the age of 5.

Strategy 1 was assumed unless otherwise stated.

8.4.1.6 Sensitivity analysis

Many of the parameter estimates or model assumptions are uncertain. The effect of changing these parameter values was assessed in a sensitivity analysis. The parameters that were varied included the duration of protection, vaccine coverage and the vaccine efficacy against VT carriage acquisition (Table 8.2). Moreover, alternative mixing patterns were also assumed and the effect of these variations on pneumococcal carriage in different age groups was assessed.

8.4.2 Results

8.4.2.1 Impact of vaccination on VT and NVT carriage prevalence

Figure 8.6 shows how vaccination might increase the carriage of non-target serotypes, while reducing the carriage of vaccine serotypes. In the case of strong competition (Figure 8.6a), non-vaccine serotypes completely replace vaccine ones slightly reducing the overall proportion of non-carrier individuals (susceptible) in the population. On the other hand, when weak or no competition between vaccine and non-vaccine serotypes is present (Figure 8.6b and Figure 8.6c), the overall effect of vaccination is to reduce the proportion of carrier through a reduction of vaccine serotypes together with a smaller increase of non-vaccine ones.

Figure 8.6 Steady state values by vaccine coverage

Fig. 8.7a - c=0.1

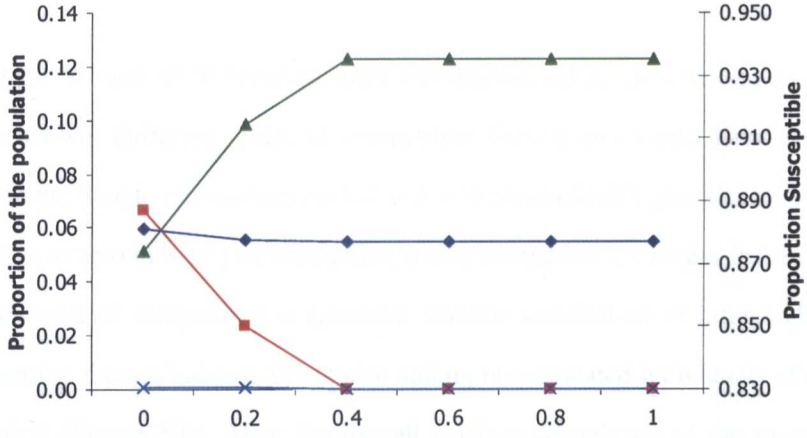


Fig. 8.7b - c=0.7

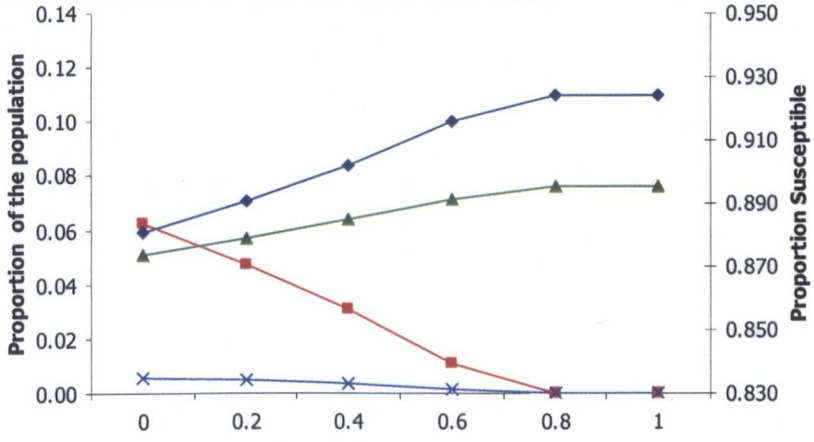
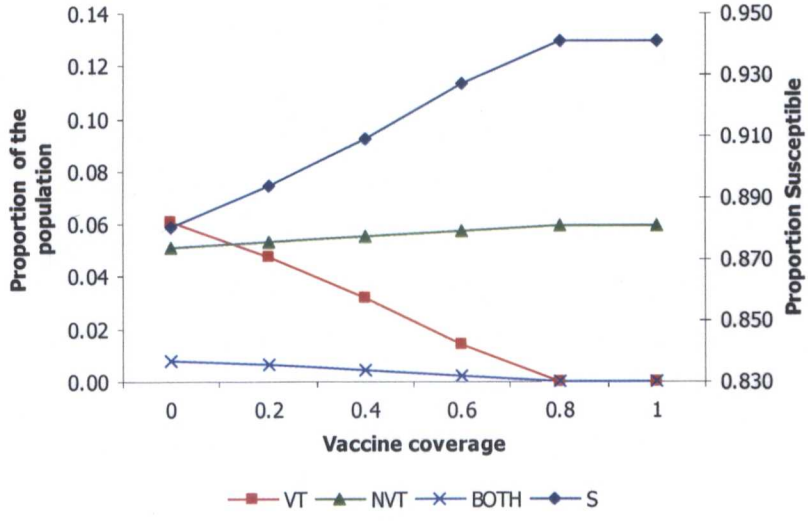


Fig. 8.7c - c=1



Moreover the existence of strong competition from non-target serotypes appears to be beneficial as it reduces the fraction of hosts that must be vaccinated in order to eliminate the target serotypes (<40% instead of 80% under base case assumptions).

In Figure 8.7 the VT and NVT dynamics after vaccination and for different levels of vaccine coverage are shown. Different levels of competition (strong and weak) have a substantial impact on both the time to elimination for VT and on the rise of NVT prevalence. VT carriage prevalence goes to zero in 9-10 years assuming strong competition, whereas in 14 years when a much lower level of competition is assumed. Routine vaccination of infants (*Strategy 1*) produces a similar, though indirect, effect also among unvaccinated individuals of older ages (herd immunity) (Figure 8.8). Also, the overall carriage prevalence of the organism may increase in some age groups (5-9 and 30+ years of age) as a consequence of vaccination, remaining stable among the 10-29 years of age (Figure 8.8c).

Figure 8.7- The effects of vaccination on the prevalence of VT and NVT, by levels of coverage and competition.

Fig. 8.8a - c=0.1

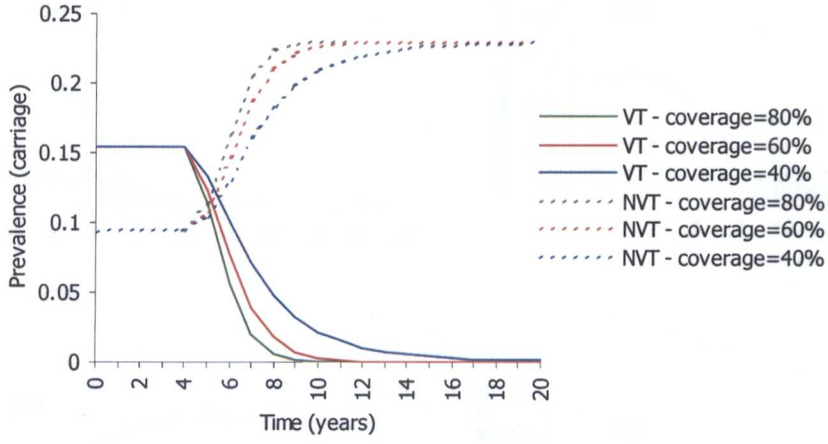


Fig. 8.8b - c=0.7

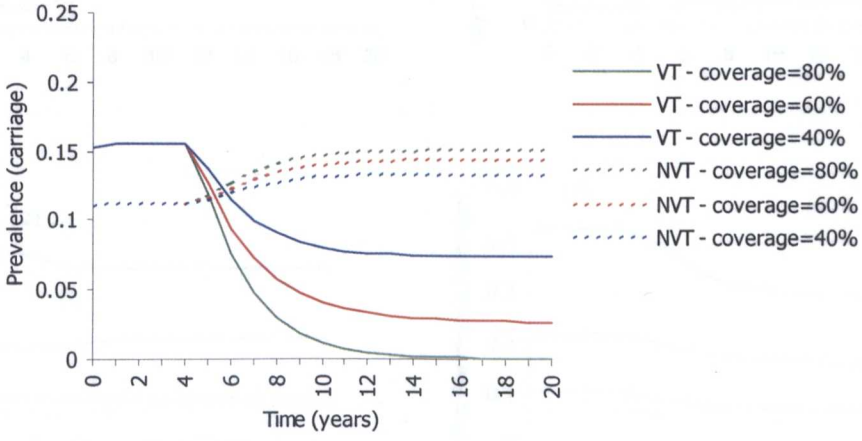
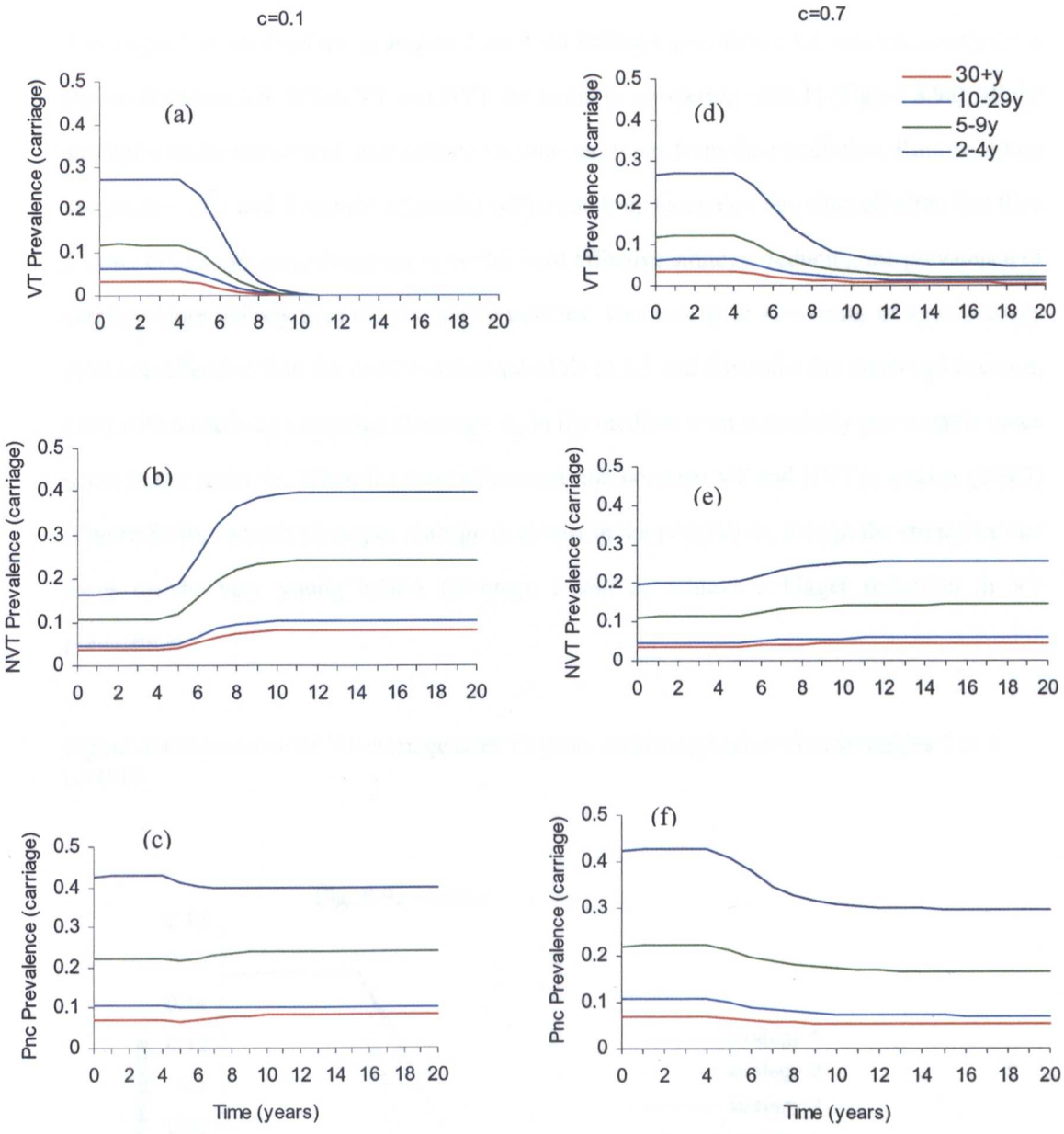


Figure 8.8- Direct and indirect effects of routine vaccination (*Strategy 1*).



8.4.2.2 Alternative vaccination programmes

The impact of vaccination strategies 1 to 4 on carriage prevalence of vaccine serotypes is shown in Figure 8.9. When VT and NVT are strongly competing (c=0.1) (Figure 8.9a), all the strategies under consideration eliminate vaccine serotypes from the circulation. Routine infant vaccination (2,3 and 4 months schedule) with a catch-up campaign targeting children less than 5 years of age (*Strategy 2*) appear to be the most effective strategy, reducing the prevalence of carriage more quickly than the alternative policies. Vaccinating at 12 months of age (*Strategy 3*) is less effective than the routine infant schedule at 2,3 and 4 months (no catch-up) because, even with a catch-up campaign (*Strategy 4*), in the medium term potentially preventable cases occur in the under 1s. When the level of competition between VT and NVT is weaker (c=0.7) (Figure 8.9b), vaccine serotypes manage to persist in the population, though the strategies that focus on the very young infants (*Strategy 1 and 2*) achieve a bigger reduction in VT prevalence.

Figure 8.9 Prevalence of VT carriage over 15 years following vaccination strategies 1 to 4 (c=0.1).

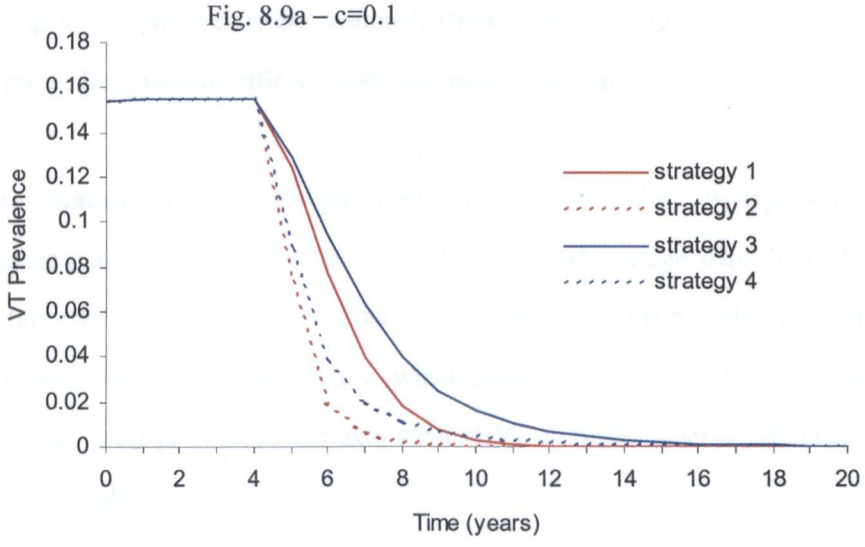
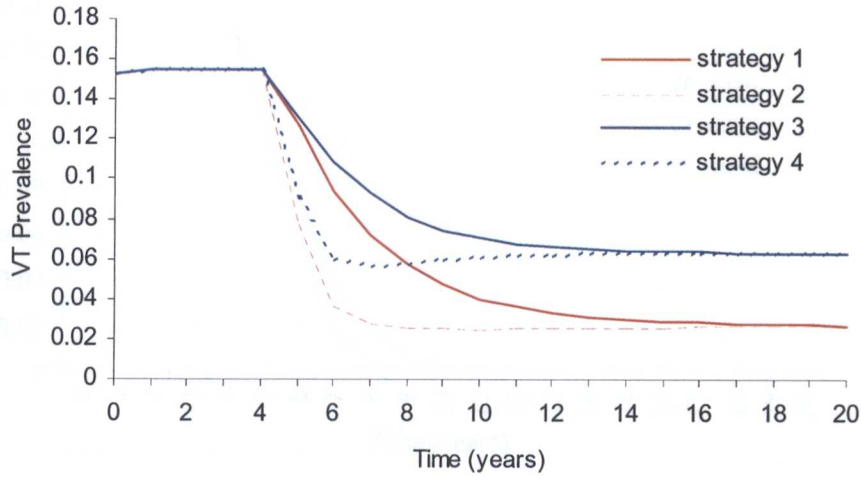


Fig. 8.9b – c=0.7

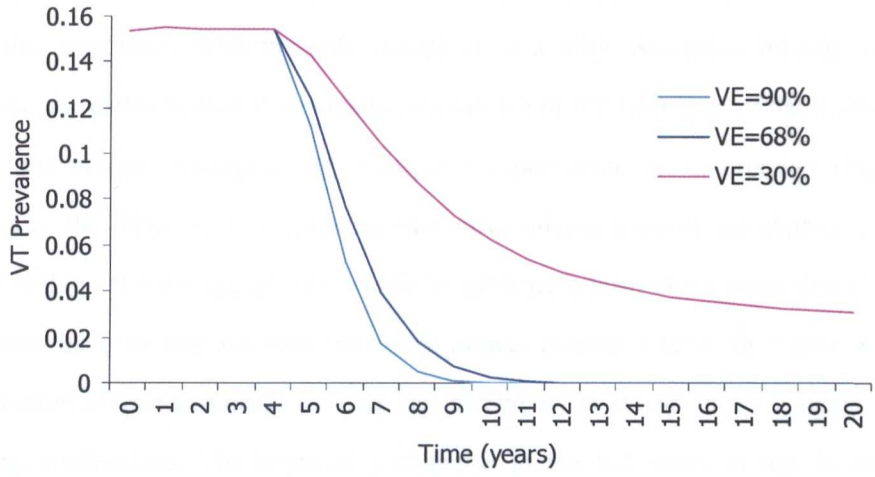


8.4.2.4 Sensitivity analysis

It is important to conduct a sensitivity analysis to assess the effect of varying the uncertain parameter estimates within their likely range (Table 8.3), especially considering that most of the vaccine related parameters were unknown. In particular, vaccine efficacy, duration of protection and mixing assumptions will be explored. Moreover, the effect of different levels of infectiousness of VT and VTv carriers is also assessed. Unless otherwise stated, the following model parameters are assumed: strong competition (c=0.1), waning rate =0.2 (5 years protection), vaccine efficacy=68% and proportional mixing (ε=0).

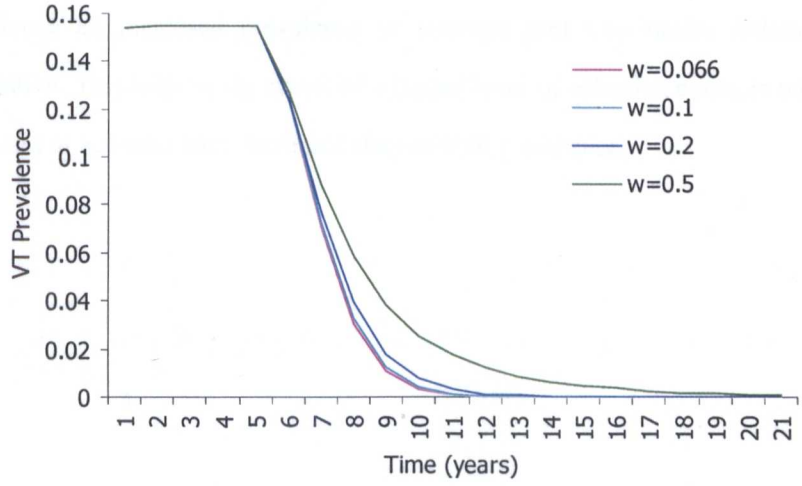
Efficacy against VT carriage acquisition. The prevalence of VT carriage is highly sensitive to changes in the assumption on vaccine efficacy against carriage acquisition. The higher the protection conferred by the vaccine, the faster the decline in the prevalence of carriage. In the case of low levels of vaccine efficacy (which could result from both vaccine failures and/or low level of direct protection), the extinction of VT carriage, under a 60% level of coverage, may not be achieved.

Figure 8.10 Carriage prevalence under different levels of vaccine efficacy (*Strategy 1*).



Waning immunity. The effect of changing the assumption on the waning rate (i.e. duration of protection of the vaccine) was investigated. If the duration of protection is short, e.g. 2 years (w=0.5), then the initial impact of the vaccination programme is similar, but the reduction in carriage prevalence is slower and VT persist for longer, though reaching elimination in around 20 years. If the duration of protection is longer, e.g ≥5 years, vaccine serotypes should disappear from circulation quicker.

Figure 8.11 Carriage prevalence under different assumptions of waning immunity (*Strategy 1*).



The above waning rates correspond to the following duration of protection: 15 (w=0.066), 10 (w=0.1), 5 (base case) (w=0.2) and 2 years (w=0.5).

Different mixing pattern. The mixing patterns of the population are perhaps one of the most difficult sets of parameters to quantify. The sensitivity analysis of the mixing parameters is therefore important. With the only exception of a fully assortative mixing, which is not realistic, the differences in the estimated prevalence of VT carriage post vaccination are small when the mixing assumption are changed (proportionate vs. assortative) (Figure 8.12a). However, the differences in adopting alternative mixing patterns are slightly more evident when looking at older age groups, which do not benefit from direct protection of the vaccine and thus have to rely on herd immunity effects (Figure 8.12b). In Figure 8.13 the age distribution of pneumococcal carriage (all serotypes) is shown under a range of different mixing assumptions. The expected prevalence in the 0-4 years of age is reduced as a consequence of vaccination. This results from the shift in the age at infection that is postponed later on in life, after the vaccine protection has waned (5 years duration of protection). This is confirmed by the slight increase in the 5-19 years old prevalence when assuming a non-fully assortative mixing. The prevalence in this age group when assuming a fully assortative pattern, however, remains at the pre vaccination levels and this may indicate that mixing between age groups is necessary in order to have an increased overall prevalence. The age group 20-29 years has a lower prevalence as opposed to the pre-vaccination era and this is probably due to the fact that carriage prevalence of non-vaccine serotype is, in this age group, lower than the one for the vaccine serotypes (Figure 8.2). Individuals aged 30+ years experience an increased prevalence of carriage post vaccination unless mixing is fully assortative. This may be the result of a higher level of effective contacts with children in the 5-9 years of age who have increased their overall prevalence.

Figure 8.12 Expected VT carriage prevalence under different mixing assumptions.

Fig. 8.12a – All ages

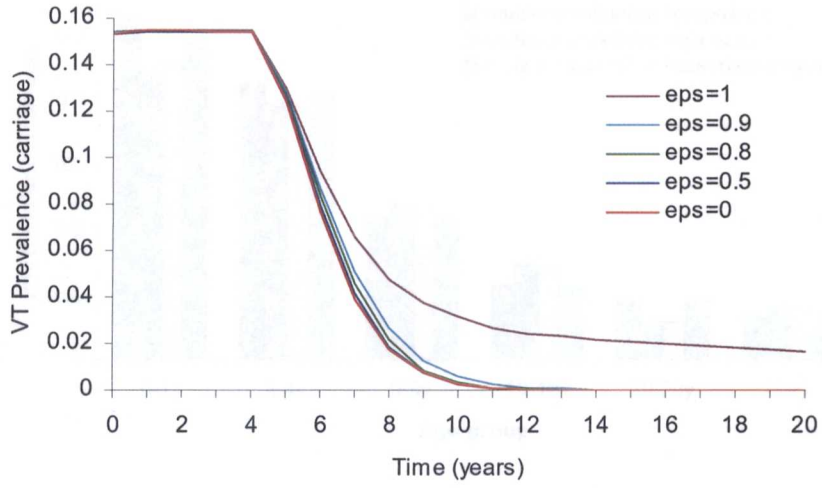
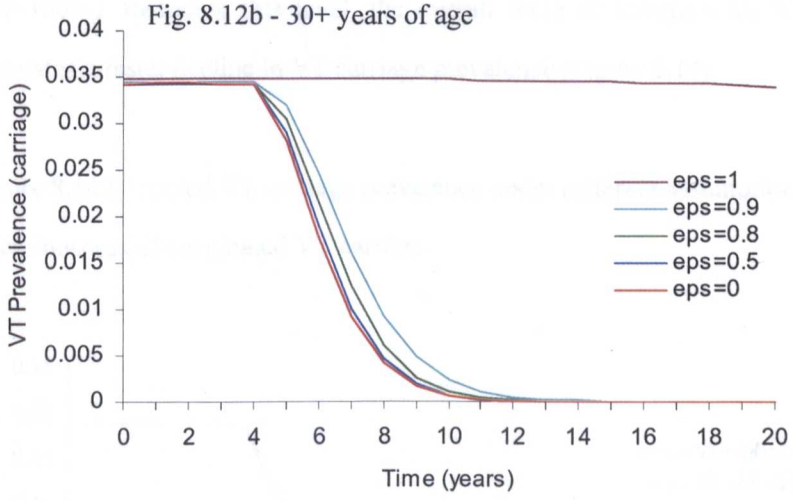
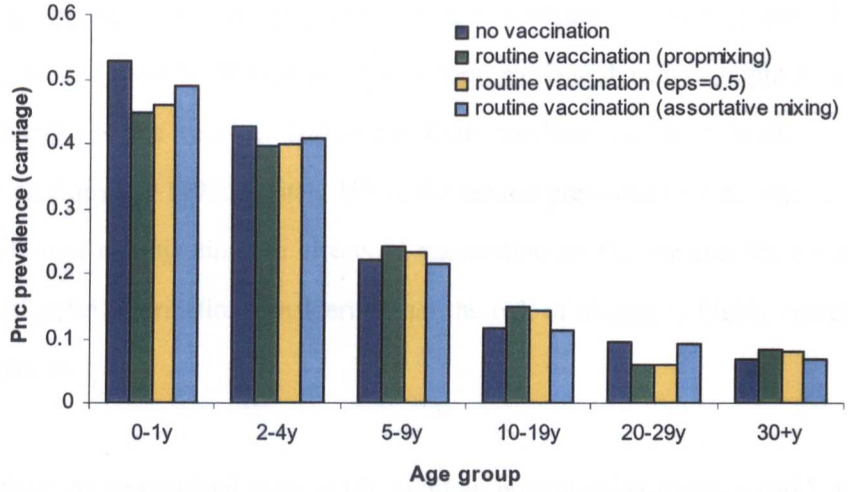


Fig. 8.12b - 30+ years of age



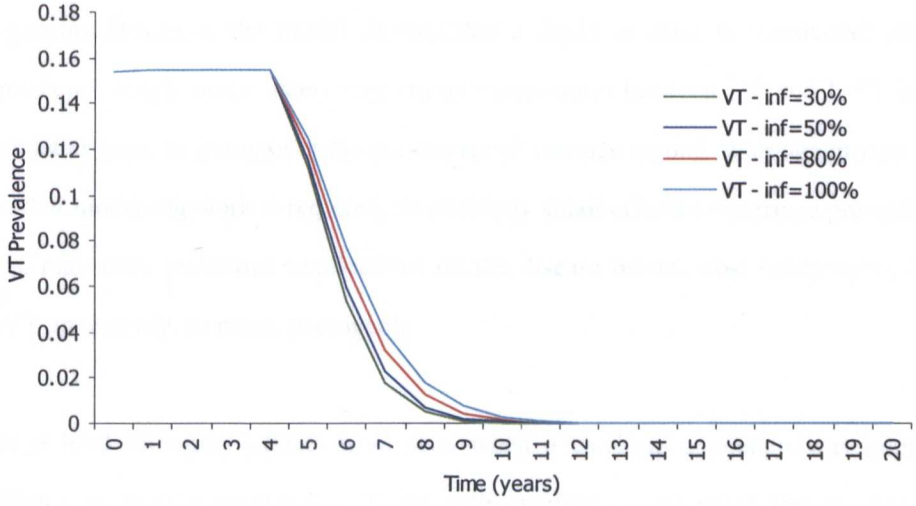
Note that eps=0 implies a proportionate mixing assumption, whereas when eps=1 a fully assortative mixing pattern is assumed

Figure 8.13 Age distribution of the estimated pneumococcal carriage prevalence under different mixing assumptions.



Infectiousness of VTv carriers as opposed to VT carriers. The effect of changing the level of infectiousness of vaccinated VT carriers as opposed to unvaccinated VT carriers was explored to test the base case assumption that these two groups were equally infectious (inf=100%). Reducing this level, the overall force of infection for VT decreases and this generates a faster decline in VT carriage prevalence (Figure 8.14).

Figure 8.14 Expected VT carriage prevalence under different assumptions on the infectiousness of vaccinated VT carriers



8.5 Discussion

These models provide useful insights into the potential effects of pneumococcal conjugate vaccination programmes at a population level. In particular, the work presented in this chapter shows how VT and NVT medium to long-term carriage dynamics might be affected by the introduction of the vaccine. Differently from previous modelling work on *S.pneumoniae* infection (Lipsitch, 1997;Lipsitch, 1999), the models presented here are age structured, which also allowed investigating the effects of vaccination on the age specific carriage estimates. This is useful information considering that the risk of disease is highly correlated with age (Chapter 3).

Data from the longitudinal study in UK families, presented in Chapter 6 and 7, were used here to derive the initial prevalence of carriage, recovery rates and the forces of infection. These allowed the estimation of the effective contact rates between different age groups and under alternative mixing assumptions.

Several alternative vaccination strategies, that may be considered if/when widespread use of the vaccine is introduced, were modelled. The predicted impact of these programmes varied according to the number of people targeted (i.e. coverage level) and the level of interaction/competition between vaccine and non-vaccine serotypes. When assuming dependence between VT and NVT, a vaccine-induced reduction of VT carriage prevalence produced an increase in carriage of NVT, though an overall reduction of the circulating organism. However, the model showed that a slight increase in the overall pneumococcal prevalence might occur when very strong competition between VT and NVT is present. In this latter case, an increase in the prevalence of carriage among older age groups was shown. Further modelling work is required, as relatively small effects on carriage prevalence, such as this, may have enormous implications on the disease burden post vaccination, especially if NVT are equally, or more, pathogenic.

Large herd immunity effects were seen when a catch-up campaign was implemented in addition to routine vaccination. These indirect effects were much less marked when only

routine vaccination was considered, although, in the short-medium term, routine vaccination of very young infants provided a better effect than routinely vaccinating one year olds with a catch-up campaign targeting children less than 5 years. Carriage prevalence rates are highest among infants less than 1 year of age and directly targeting this age group has a disproportionate effect on the overall prevalence. Although the strategies that were simulated here are those that might be considered in the UK if the recommendation will be implemented, these models are flexible and can be adapted to consider any vaccination strategy for any country of interest. An optimal immunisation policy is based on the epidemiology experienced in the country under consideration, which, in turn, is a result of the intrinsic characteristics of the organism, pathogen-host relation and, most importantly, mixing patterns.

The outputs of the model are certainly limited by the quality of the parameter estimates and model assumptions. In this chapter some efforts have been made to fit the model parameters to data from the longitudinal study and also to assess the sensitivity of the model to changes in the parameter values. Model results were shown to be highly sensitive to changes in the level of competition between VT and NVT. But the model simplistically assumes that competition is perfectly symmetric ($c_V=c_N$), and as this clearly represents a crucial process in the dynamics of pneumococci, this effect may well dominate the outcome of any vaccination programme. More work should be done on investigating further different kinds of competition rather than just considering a reduced susceptibility to infection when already colonised. Zhang and colleagues (2004) using a transmission dynamic non age structured model investigated different forms of competition (i.e. direct and indirect). The authors demonstrated that direct (physical) competition between two serotypes only influences the prevalence of carriers if the duration of naturally acquired immunity is small, whereas indirect (antibody mediated) competition is only of influence if naturally acquired immunity is long lasting. Whether there is any age related effects in these relationships still remains an open question which deserves some attention, as both the duration of carriage and the risk of disease are both highly age-dependent.

Moreover, the reduction in the risk of being co-colonised may depend on the specific serotype that is already present in the nasopharynx (rather than VT or NVT as was considered here). Analysis of this issue was performed in Chapter 7 where diverse serotype-specific patterns were shown. An individual based model should be considered if aiming to study this subject further as only a model of this kind could incorporate the diversity that may be present. Similarly, an individual based model could also improve other limiting aspects of the current model, i.e forces of infection and recovery rates. Here serotypes included in the vaccine are assumed to be completely identical in terms of transmissibility and, similarly, serotypes that are not included have the same force of infection. It is well known, and has been shown in Chapter 7, that serotypes are extremely diverse and that also transmissibility may be serotype-specific. Also, recovery rates are assumed to be age dependent but the same for VT and NVT. Again, this was a necessary simplification and alternative assumptions could be explored with a different type of model.

Another major potential limiting factor is the assumptions made about the mixing pattern in the population, as the true mixing patterns are unknown. This is a very critical point that refers not only to the particular model developed here, but also to any model of this kind. Edmunds and colleagues (1997) attempted to measure the contact patterns directly, through questionnaire based methods. A larger study using similar method has recently been conducted in both rural and urban settings, although these results are not yet available (Dr W. John Edmunds, personal communication).

Assessing the effects of vaccination on pneumococcal disease is certainly the final outcome of interest. More work will be done on including different forms of clinical conditions that may derive from an episode of carriage. This will allow first validating the model assumptions comparing results to data that will continue to be available from surveillance systems. Secondly, incidence rates under alternative intervention programmes will be generated and used in economic analyses to assess the cost-effectiveness of the vaccination programmes and provide advice to policy decision makers.

This type of analysis may be very useful for countries that are considering the introduction of the conjugate vaccine. In addition, these models can be adapted to look at different vaccination strategies for the UK and this will be extremely valuable as more information on the observed effects of the UK campaign may improve the parameter estimates of the model. The experience with the Hib and MencC vaccines (Trotter *et al.*, 2003;McVernon *et al.*, 2004;Trotter *et al.*, 2004) showed that the post-vaccine era may be far from straightforward and that continued monitoring of the effects of vaccination on carriage and on the duration of vaccine efficacy may be critical to the success of the pneumococcal conjugate vaccine programme.

In the following chapter, economic analysis of the conjugate vaccine will be performed. The indirect effects of the vaccine, which have been shown to be so crucial in the long-term dynamics of pneumococcal carriage post vaccination, will be included and their impact on the cost-effectiveness of alternative vaccination programmes will be assessed.

CHAPTER 9 - COST-EFFECTIVENESS ANALYSIS OF PNEUMOCOCCAL CONJUGATE VACCINATION IN ENGLAND AND WALES

9.1 Aims

- To assess the cost-effectiveness of PCV vaccination in England and Wales;
- To estimate the cost-effectiveness of a range of alternative strategies that may be considered when a vaccination programme is introduced;
- To investigate the impacts that herd immunity effects and serotype replacement mechanism may have on the overall cost-effectiveness of the programme.

9.2 Introduction

The importance of economic evaluation for the design of vaccination policies has already been discussed in Chapter 5 where the then current UK vaccination programme with PPV was evaluated and the cost-effectiveness of vaccinating all the elderly assessed. A separate analysis, however, is necessary for the 7-valent pneumococcal conjugate vaccine (PCV) which was licensed in the UK in 2001 and is currently only recommended to infants aged between 2 months and 5 years who are at special risk (Salisbury & Begg, 1996). Although evidence of the direct effect of the 7-valent vaccine on the incidence of Pnc disease (invasive pneumococcal disease (IPD), pneumonia and AOM) among healthy children has been shown (Chapter 2) as well as an indirect effect among unvaccinated individuals (Whitney *et al.*, 2003), changes in the prevalence of carriage of vaccine *versus* non-vaccine types has also

been observed among vaccinated individuals (Dagan *et al.*, 2002) and also among their siblings (Givon-Lavi *et al.*, 2003). A reduction of carriage of vaccine serotypes in the population, as a consequence of the introduction of PCV, may induce other serotypes not contained in the vaccine to occupy their ecological *niche*. Whether this change will have a positive or negative overall effect at the population level is not straightforward as it depends on the serotypes that are taking over (which may vary in different geographical regions), their relative invasiveness as well as the host response to their presence. These indirect effects of the vaccine are crucial aspects not only when considering the biology of *S.pneumoniae* infection and the transmission dynamics in the population, but also when performing cost-effectiveness analysis of the alternative vaccination programmes. However, as very little information is available at the time of this analysis on these longer-term effects of the vaccine, alternative potential scenarios have to be considered and their effects on the economic analysis assessed.

This chapter addresses the issue of whether universal infant vaccination with the 7-valent pneumococcal conjugate vaccine (PCV) would be a cost-effective policy under the health care provider perspective (NHS). The analysis takes into consideration the various uncertainties related to the burden of pneumococcal disease and the potential for indirect protection (herd immunity) among unvaccinated individuals as well as serotype replacement effects in the whole population. Different UK vaccination schedules are considered in the analysis as well as the sensitivity of the model result to variations in the vaccine price. This work has been published (Melegaro & Edmunds, 2004c).

9.3 Methods

9.3.1 Cohort model

A model was constructed to follow a vaccinated and an unvaccinated imaginary cohort of individuals from birth until death. The number of life-years (LY) gained from the vaccination programme was taken as the primary measure of the outcome of the programme, and this was compared to its net cost (the net cost being the additional cost of vaccination minus the

expected savings from the programme in terms of reduced use of health care resources). Although pneumococcal infection can result in a wide range of outcomes such as invasive disease, pneumonia, ear infections, sinusitis, bronchitis, arthritis, conjunctivitis, peritonitis, etc., the model only considers the four major outcomes for which clinical trial data are available regarding vaccine efficacy: pneumococcal meningitis, pneumococcal bacteraemia, community-acquired pneumonia (CAP) and AOM. Future benefits and costs were discounted according to the current recommendations in the UK (HM Treasury, 2003): 3.5% per annum for costs and 1.5% per annum for health benefits. Herd immunity, i.e. changes in disease incidence among unvaccinated individuals, is included as part of the scenario analyses (section 8.3.6) as well as changes in carriage and serotype distribution that may be expected to occur after the introduction of pneumococcal vaccination. These two scenarios are further investigated in the multivariate (probabilistic) sensitivity analysis.

9.3.2 Epidemiological data

The epidemiological parameters used in the base case analysis, are shown in Table 9.1 and Table 9.2. For the base case analysis the average annual incidence of both pneumococcal bacteraemia and meningitis was derived extracting the number of invasive pneumococcal disease cases that was reported to the reconciled CDSC/RSIL database (Miller *et al.*, 2000;George & Melegaro, 2001) (Chapter 3) for the period 1998-2000 and dividing it by the ONS population estimates for England and Wales and for the same time period.

Age specific incidence rates were used in the model, using 5-year age bands except in those under 1 year of age, which were grouped in one age category. In the univariate sensitivity analysis (section 8.3.6) the effect of a further age stratification (<6 mths, 6-11 mths) is explored. The case-fatality ratio (CFR) and the average length of stay (LOS) in the hospital for IPD cases were derived from Hospital Episodes Statistics (HES) (Department of Health, 2003), using number of deaths and length of stay of all pneumococcal septicaemia (ICD-10 Code: A403) and pneumococcal meningitis (ICD-10 Code: G001) patients, as reported in the first diagnostic field for the period April 1997 to March 2000 (Table 9.2).

Table 9.1 - Estimated annual incidence of pneumococcal related diseases, hospitalisations, and GP consultations in England and Wales.

	Incidence rate[a]		Hospitalisations rate[b]		GP consultation rate[c]	
Age group	Pnc bacteraemia	Pnc meningitis	Pneumonia with +film	AOM	Pneumonia	AOM
<1	27.3	14.6	221.2	173.2	467	23,636
1-4	10.6	1.6	131.2	203.2	272	24,856
5-9	1.9	0.2	41.7	123.9	62	7,698
10-14	0.7	0.2	17.2	34.3	62	7,698
15-19	1.2	0.1	16.3	13.1	51	2,250
20-24	1.8	0.2	18.1	7.5	51	2,250
25-44	3.1	0.3	26.0	9.1	152	1,741
45-64	6.5	0.5	55.4	11.7	268	1,175
65-74	18.7	0.9	193.6	11.0	508	994
75+	42.5	0.6	697.7	7.5	1,161	520
Overall	8.4	0.6	102.7	30.5	266	3,612

All rates are per 100,000 populations per year. [a]CDSC/RSIL; [b]Hospital Episode Statistics, first diagnostic field (ICD-10 codes for pneumonia: J13, J180, J181, J188, J189; any otitis media codes used for OM hospitalisations); [c]Royal College of General Practitioners (Fleming DM, 1999).

Table 9.2 - Estimated case fatality ratios and length of stay in the hospital.

Age group (years)	Case-fatality ratio			Length of stay (days)		
	Pnc septicaemia	Pnc meningitis	Pneumonia	Pnc septicaemia	Pnc meningitis	Pneumonia
<1	4%	4%	1%	5.4	10.5	4.4
1-4	1%	4%	0%	4.6	10.2	2.9
5-9	0%	3%	1%	13.1	9.4	3.2
10-14	0%	0%	2%	6.8	7.2	4.0
15-19	0%	11%	2%	11.0	8.9	4.9
20-24	8%	0%	3%	4.7	12.5	5.0
25-44	20%	11%	3%	12.3	14.3	6.0
45-64	26%	18%	14%	12.7	22.1	9.0
65-74	27%	29%	29%	11.3	20.9	11.8
75+	40%	43%	46%	15.4	25.8	15.4
Overall	22%	12%	29%	11.5	16.9	8.1

Admitted patients reporting Pnc septicaemia (ICD-10 code: A403), Pnc meningitis (G001) or pneumonia (codes as in Table 1) in the first diagnostic field.

The number of hospitalisations for CAP was estimated from HES, extracting all records that were reporting one of the following ICD-10 pneumonia codes in the first diagnostic field over the period April 1995 to March 1998:

- Pneumococcal pneumonia: J13 (ICD-9: 481)
- Lobar pneumonia, organism unspecified: J181 (ICD-9: 481)

- Bronchopneumonia, organism unspecified: J180 (ICD-9: 485)
- Other pneumonia, organism unspecified: J188 (ICD-9: 486)
- Pneumonia, organism unspecified: J189 (ICD-9: 486)

Based on a study by Djuretic and colleagues (1998), 79% of these admissions were assumed to present with lobar/focal changes and thus were considered in this analysis in order to match as closely as possible the case definition that was used in the Kaiser Permanente trial (Black *et al.*, 2002) to estimate the level of vaccine efficacy. Base case age specific hospitalisation rates were thus derived dividing the number of hospital admissions (first diagnosis) by ONS population estimates for England (Table 9.1). CFR and the average LOS in hospital for patients with pneumonia were calculated from the extracted data. The annual GP consultation rates for pneumonia were derived from the Royal College of General Practitioners (RCGP) Weekly Returns Service (Fleming DM, 1999) (Chapter 2 and 3).

Acute otitis media hospitalisation rates were derived from HES extracting any hospitalisation with AOM ICD-10 codes (H650-H678) in the first diagnostic field over the 1999-2000 HES financial year and dividing it by the corresponding ONS population estimates for England. RCGP data were used to derive GP consultation rates for AOM.

9.3.3 Vaccine efficacy

In the base case analysis the vaccine was assumed to give no protection against pneumococcal carriage and, thus, no indirect effects such as herd immunity and serotype replacement were considered. This scenario appears to be unrealistic, as some protection against carriage and serotype replacement has been observed on pneumococcal carriage and disease (Chapter 2). Quantifying the long-term impact of these processes is, however, difficult, hence in the base-case these indirect effects of the vaccine will be ignored. Vaccine efficacy (VE) against pneumococcal disease was based on intention to treat results of recent clinical trials and for IPD this was adjusted to reflect the differing serotype distribution in the UK compared with the population in Northern California at the time of the study (Black *et al.*, 2000). The base

case VE against IPD was therefore 63-87% in the first five years of life. VE against all cause clinical pneumonia with a positive film was assumed to be 17.7% (95%CI: 4.8 to 28.9) (Black *et al.*, 2002); and VE against any confirmed otitis media was 7% (95%CI: -5% to 17%) (Eskola *et al.*, 2001). Note also that due to the lack of data on serotype distribution of otitis media and pneumonia cases, we do not adjust the VE estimates for these conditions. It is assumed, in the base case, that children who respond to the vaccine become protected at 4 months of age after 3 doses of vaccine have been given (accelerated infant schedule). Prior to this age, they are unprotected. In addition, the following alternative schedules were also considered: 3 doses with the protection starting at 6 months of age (non-accelerated infant schedule); 2 doses with the protection effective from 6 months of age; and 1 dose at one year of age. Note that in the trials three doses plus a booster were used whereas in the above schedules one to three doses of vaccine are given, and it is assumed that the reduced dosage does not reduce vaccine efficacy. Results of phase 2 trials with pneumococcal conjugate vaccine in UK infants and toddlers demonstrated that 2 doses of PCV given at 2 and 4 months of age provide satisfactory primary immunogenicity to the serotypes contained in Prevenar (Goldblatt *et al.*, 2004). Incremental cost-effectiveness ratios were calculated for each successive alternative, from the least costly to the most, examining the additional costs that one programme imposes over another, compared with the additional benefits it delivers (Drummond *et al.*, 1997). Clearly, if vaccine efficacy of the different schedules is the same, and protection starts at the same age, then the schedule with the lower number of doses will be preferred. Finally, in the base case we assume a 10-year period of vaccine-induced protection against disease although in the univariate sensitivity analysis the effect of changes in the duration of protection on the model results were assessed.

9.3.4 Health outcomes

The primary outcome measure was discounted life-years gained. Pneumococcal specific case fatality ratios were calculated from hospitalisation data (see above). Fatal cases were assumed to lose the average life expectancy for individuals of that age. Life expectancy calculations were derived from current all-cause mortality schedules, derived from ONS tables.

The secondary outcome measure was discounted Quality Adjusted Life-Years (QALY) gained which can simultaneously capture gains from reduced morbidity (quality gains) and reduced mortality (quantity gains) and integrates these into a single measure (Drummond *et al.*, 1997). Reductions in health related quality of life due to pneumococcal disease (calculated on a 0-1 scale where 1 is equivalent to perfect health) were derived from the literature and are summarised in Table 9.3.

Table 9.3 - Outcome from a meningitis episode and QALY lost of pneumococcal diseases

Outcomes from meningitis	**% Children**	**Source**
Severe bilateral hearing loss	14	(Hussain *et al.*, 2003)
Other sensorineural hearing loss	16	(Hussain *et al.*, 2003)
Conductive hearing loss	19	(Hussain *et al.*, 2003)
Seizures	16	(Hussain *et al.*, 2003)
Outcomes from Pnc diseases	**QALY loss**	
Bacteraemia	0.0079[b]	(Bennett et al., 2000)
Meningitis	0.0232[b]	(Bennett et al., 2000)
- Bilateral hearing loss (first year)	0.460[a]	(Cheng & Niparko, 1999)
- Bilateral hearing loss (subsequent years)	0.200[a]	(Cheng & Niparko, 1999)
- Other hearing loss (all subsequent years)	0.100[a]	(Oostenbrink *et al.*, 2002)
Pneumonia		
- Outpatient	0.004[b]	(Vold & Owens, 2000)
- Inpatient	0.006[b]	(Vold & Owens, 2000;Bennett *et al.*, 2000)
OM	*0.005*[b]	(Oh et al., 1996)

[a]*per year;* [b]*per episode*

A recent study (Prosser et al., 2004) has suggested that the QALY's lost due to acute pneumococcal disease are far greater than the values used here. These estimates were not used in the current analysis as they are orders of magnitude greater than the other estimates available in the literature. Note that due to the paucity of data, the proportion of IPD patients developing sequelae and the QALY weights attached to these were assumed not age-dependent. This is unlikely to be the case. However, it will only affect the results of the herd immunity scenario (see below), as direct vaccine-induced protection is not assumed to be life-long. As the elderly are more likely to have pre-existing morbid conditions, the QALY loss from the herd-immunity scenario is likely to be overestimated. Other outcome measures include GP consultations avoided, hospitalisations avoided and deaths avoided.

9.3.5 Costs estimates

The perspective of the study was the health care provider (NHS). Costs to the patient and their carers (i.e. absenteeism, travel to clinics etc) were ignored because of a lack of data on the wider (societal) costs of pneumococcal disease in the UK. Average unit costs estimates of, for instance, an inpatient day and GP consultation, were taken from standard sources and are listed in Table 9.4. The cost per vaccine dose was set to £30, assuming a volume based discount of approximately £9 (list price of the vaccine is £39.25 per dose (British Medical Association, 2002). The cost per infant of vaccination was calculated multiplying the cost of a vaccine dose by the number of doses and making an additional allowance of £10 per child per dose (nurse consultation cost (Netten & Curtis, 2002)) for the administration of the schedule. All costs were measured in pounds sterling at 2002 prices. The average cost of a meningitis case was derived from a case notes review of all meningitis cases <5 years age from 4 regions reported to CDSC/RSIL between 1996 and 1999 (Hussain *et al.*, 2003). This was calculated considering the proportion of patients that experienced different types of sequelae (Table 9.3) and estimating their related cost using standard sources (Netten & Curtis, 2002;Hussain *et al.*, 2003). Similarly, an additional annual cost to the health service was estimated for the subsequent years considering the additional visits and therapies resulting from chronic sequelae of pneumococcal meningitis. Hospitalisation cost for otitis media included the cost of minor ear procedures (most would be tympanostomy) and one ENT outpatient visit. All costs were varied in the sensitivity analysis between +/-25% of their base case values.

Table 9.4 - Unit costs of care and treatment parameters.

Parameter	Base Value (Range)	Source
Cost per vaccine dose		
- Cost of vaccine (£)	30 (22-37)	(British Medical Association, 2002)
- Administration cost (£)	10 (7-12)	(Netten A & Curtis L, 2002)
- Number of doses	3	
Cost per inpatient day		
- Mean cost of inpatient day (general ward) (£)	273 (205-341)	(Netten A & Curtis L, 2002)
- Mean cost of inpatient day (paediatrics) (£)	398 (298-497)	(Netten A & Curtis L, 2002)
- Mean cost of intensive care bed/day (£)	1,232 (924-1540)	(Department of Health, 2002)
- Mean cost of paediatric intensive care bed/day (£)	1,384 (1038-1730)	(Department of Health, 2002)
Mean length of stay in hospital		
- Bacteraemia (days)	11 (variable by age)	HES
- Meningitis (days)	17 (variable by age)	HES
- Pneumonia (days)	8 (variable by age)	HES
Proportion of bed-days on intensive care (adult)		
- Bacteraemia (%)	5 (3.7-6.2)	HES
- Meningitis (%)	10 (7.5-12.5)	HES
- Pneumonia (%)	1 (0.7-1.2)	HES
Proportion of bed-days on intensive care (child)		
- Bacteraemia (%)	3 (2.2-3.7)	HES
- Meningitis (%)	6 (4.5-7.5)	HES
- Pneumonia (%)	0	HES
Other costs (acute stay)		
Bacteraemia & Pneumonia		
- X-Ray (£)	16 (12-20)	(Department of Health, 2002)
Meningitis		
- CT scan (£)	89 (67-112)	(Department of Health, 2002)
- Cranial ultra-sound (£)	51 (38-64)	(Hussain *et al.*, 2003)
- Follow-up (Exc. Sequelae) (£)	103 (77-129)	(Department of Health, 2002)
- MRI (£)	270 (203-338)	(Department of Health, 2002)
Otitis media		
- Ear procedures (£)	517 (388-646)	(Department of Health, 2002)
- Outpatient ENT consultant visit (£)	52 (39-65)	(Department of Health, 2002)
Proportion undergoing different procedures		
- CT scan (adult) (%)	100	(Hussain *et al.*, 2003)
- CT scan (child) (%)	46	(Hussain *et al.*, 2003)
- MRI (%)	9	(Hussain *et al.*, 2003)
- Cranial ultrasound (child) (%)	30	(Hussain *et al.*, 2003)
General practice consultation and treatment costs		
- Cost per general practice consultation (£)	19 (14-24)	(Netten A & Curtis L, 2002)
- Mean cost of treatment per consultation - IPD (£)	8 (6-10)	(British Medical Association, 2002)
- Mean cost of treatment per consultation - Pneumonia (£)	4 (3-5)	(British Medical Association, 2002)
- Mean cost of treatment per consultation - OM (£)	2 (1.5-2.5)	(British Medical Association, 2002)
Average cost of a meningitis case		
- First year (£)	4,703 (3,528-5,880)	(Hussain *et al.*, 2003)
- Subsequent years (£)	143 (113-189)	(Hussain *et al.*, 2003)
Discount Rates		
- Discount Costs	3.5%	(HM Treasury, 2003)
- Discount Benefits	1.5%	(HM Treasury, 2003)

9.3.6 Sensitivity and scenario analysis

The most likely parameters values were used in the base case scenario. However, a univariate sensitivity analysis was also performed looking at the effect of changing one parameter at a time within its given range.

In addition to the sensitivity analyses and due to the high level of uncertainty that characterise the current and future burden of pneumococcal disease, the following three scenarios were also considered:

a) **High incidence scenario.** A capture-recapture study (Gjini *et al.*, 2004), estimated the sensitivity of CDSC/RSIL for the diagnosis of pneumococcal meningitis in adults (mean age 55, range 16-97 years) to be 40% (95%CI: 37-44). Incidence rates were thus inflated to take into account possible under ascertainment. For hospitalised pneumonia, incidence rates were inflated by including the following additional codes [ICD-10: J158 (other bacterial pneumonia) and J159 (bacterial pneumonia unspecified)]; any code for pneumonia in any diagnostic field (i.e. not necessarily primary diagnosis); and assuming that all admissions for pneumonia resulted in a positive film (rather than the estimated 79%). For AOM hospitalisations, any AOM codes in any diagnostic fields were considered. An upper estimate of both pneumonia and AOM GP consultation rates was obtained using MSGP4 data (Chapter 3).

b) **Inclusion of herd immunity effects.** Whitney and colleagues (2003) recently published estimates of the reduction in IPD incidence in the US in unvaccinated age groups following the introduction of the pneumococcal conjugate vaccine in infants. They estimated the following reduction in IPD incidence among unvaccinated individuals: 32% (95%CI 23%-39%) in the 20-39 years old, 8% (95%CI 1%-15%) in the 40-64 years and 18% (95%CI 11%-24%) in the 65+ roughly 1 year after the introduction of infant vaccination. We allowed for these changes in invasive disease incidence and assumed that a similar indirect effect occurs on the proportion of

pneumonia and otitis media cases attributable to a pneumococcal infection (assumed, respectively, 48% (Lim W.S. *et al.*, 2001b) and 30% (Jacobs *et al.*, 1998;Palmu *et al.*, 2004)). The effect of changes in these proportions was considered in both the univariate and multivariate sensitivity analyses. Since the period of protection against carriage appears to be short (Lakshman *et al.*, 2003) we assumed that vaccination of one infant cohort would reduce the carriage of pneumococci, and thus the incidence of disease, in other age groups for one year.

c) **Serotype replacement**. Serotype replacement of vaccine types with non-vaccine types has been observed in both pneumococcal carriage (Dagan *et al.*, 2002;Dagan *et al.*, 2003) and disease (Eskola *et al.*, 2001;Veenhoven *et al.*, 2003;Kaplan *et al.*, 2004). The potential effect of a complete substitution of vaccine types with non-vaccine ones on the cost-effectiveness of the programme is explored in this scenario analysis reducing both the direct effect of the vaccine among vaccinated individuals as well as the indirect effect (herd immunity as in scenario (b)) produced among unvaccinated ones (Whitney *et al.*, 2003). The percentage substitution of vaccine types with non-vaccine types, which in this scenario is set to 100% (i.e. complete substitution), is referred to in the following text as the *serotype replacement coefficient* (SRC). The severity of non-vaccine types in causing IPD is derived from Brueggemenn and colleagues (2003) study, calculating the non-vaccine vs. vaccine types odds ratio (OR) after adjusting by the serotype-specific duration of carriage reported in Smith and colleagues (1993) (OR=0.16, 95%CI: 0.10-0.25). Non-vaccine serotypes are assumed to be equally severe in causing CAP and AOM (OR=1).

Note that whereas scenario (a) still maintains the assumption that the vaccine does not produce indirect effects, i.e. no protection against pneumococcal carriage, and simply considers a change in the incidence rates of pneumococcal disease, scenarios (b) and (c) allow the indirect effects of the vaccine at the population level to occur. In particular, scenario (b) considers a reduction in pneumococcal disease among unvaccinated individuals as a consequence of a reduction in carriage. Scenario (c) includes both the herd immunity effect as

well as a change in the serotype distribution of pneumococcal carriage, which also produces an effect on pneumococcal disease.

A multivariate sensitivity analysis was also performed using Monte Carlo simulation with @Risk 4.0 (Palisade Corporation, NY, USA) and drawing input parameter values from probability distributions using Latin Hypercube sampling. Uniform distributions were assumed for age-specific incidence rates, case-fatality ratios and length of stay in the hospital as well as for all the parameters related to the cost of care and treatment. For incidence estimates the lower limit was set to be the base case and the upper limit was set to the high incidence scenario (scenario a). CFRs and LOS were varied between +-25% of their base case values. The SRC was assumed to follow a triangular distribution with a mode of 1, and range of 0-1. A normal distribution was assigned to the log OR estimated from the vaccine trials (Black *et al.*, 2000;Eskola *et al.*, 2001;Black *et al.*, 2002) and from which the levels of protection were derived (VE=1-OR). The proportion of CAP and AOM cases caused by *S.pneumoniae* (48% and 30% respectively in the base case) was assumed to follow a binomial distribution with variance determined by the sample sizes of the original studies (Jacobs *et al.*, 1998;Lim W.S. *et al.*, 2001a). The herd immunity effect was kept constant at 5% in three out of the five scenarios explored in the multivariate analysis. The other two scenarios considered were the base case, where no herd immunity and no serotype replacement effect were included, and the Whitney scenario where age-specific indirect protection was assumed to vary within the reported 95% confidence intervals (Whitney *et al.*, 2003). A distribution of outcome values was generated running the model 1000 times and the results are presented for different levels of herd immunity and under different assumptions on the level of serotype replacement.

9.4 Results

9.4.1 Current burden of disease

Table 9.5 gives the estimated current burden of IPD, all-cause pneumonia and otitis media in England and Wales. There are an estimated 2 million GP visits, almost 76 thousand hospital admissions and over 17 thousand deaths per year (most of which are attributable to pneumonia in the elderly). The health burden in children less than 15 years of age is large with 46% and 75% of hospital admissions due to, respectively, meningitis and otitis media falling in this age group as well as 62% of GP visits. The estimated cost to the health service related to these outcomes is given in Table 9.6. In children an estimated 76% of the overall cost is due to treating otitis media.

From these estimates and assuming that 48% and 30% are the proportions of, respectively, pneumonia and AOM due to *S.pneumoniae* (Lim *et al.*, 2001;Pelton, 2001), the burden of pneumococcal specific disease consists of over 650,000 GP consultations, 36,000 hospital admissions (IPD and non-IPD) and around 9,000 deaths in England and Wales per year.

Table 9.5 - Estimated current burden of IPD, pneumonia and otitis media in England and Wales.

Current Burden (England & Wales)	**All ages**	**Under 15**
GP visits	**2,083,882**	**1,346,110**
- Pneumonia	142,017	14,547
- OM	1,941,865	1,331,563
Admissions	**75,720**	**19,989**
- Bacteraemia	4,407	544
- Meningitis	324	148
- Pneumonia	54,373	6,904
- OM	16,616	12,394
Deaths	**17,334**	**63**
- Bacteraemia	1,225	11
- Meningitis	45	6
- Pneumonia	16,064	46

Pneumonia=all cause pneumonia with lobar/focal change; OM=all cause OM

Table 9.6 - Estimated cost of the current burden of pneumococcal disease from the health care payer perspective, England and Wales.

	All ages	Under 15
GP visits (total)	**£44,021,605**	**£28,306,271**
- Pneumonia	£3,223,027	£330,142
- OM	£40,798,578	£27,976,129
Acute admissions (total)	**£212,275,776**	**£16,552,586**
- Bacteraemia	£18,645,033	£1,424,670
- Meningitis	£3,873,214	£1,415,882
- Pneumonia	£180,303,253	£6,660,063
- OM	£9,454,276	£7,051,971
Sequelae for meningitis	**£3,073,240**	**£1,052,566**
Total	**£259,370,621**	**£45,911,423**

9.4.2 Base case results

The estimated reduction in the burden of disease due to the vaccination programme is shown in Table 9.7. The programme with base case parameters is estimated to prevent almost 63,000 GP consultations, 1890 hospital admissions and 14 deaths, resulting in a total of 1087 undiscounted life-years and 1824 undiscounted QALYs gained in the vaccinated cohort over their life-span (at 1.5% discount rate these are 629 and 1188 respectively).

Table 9.7 - Undiscounted health outcomes and estimated reduction of disease burden in the vaccinated cohort.

	No vaccination	With vaccination	Difference
Deaths (total)	**19,346**	**19,331**	**14**
Deaths Bacteraemia	1,307	1,301	6
Deaths Meningitis	46	42	3
Deaths Pneumonia	17,993	17,988	5
Hospital's (total)	**77,492**	**75,602**	**1,890**
Hosp Bacteraemia	4,567	4,264	302
Hosp Meningitis	318	239	79
Hosp Pneumonia	57,527	56,632	894
Hosp OM	15,081	14,467	614
GP consult (total)	**1,952,942**	**1,889,987**	**62,955**
GP consult Pneumonia	141,952	140,211	1,741
GP consult OM	1,810,990	1,749,776	61,215

The base-case programme is estimated to have a net discounted cost to the health service of £71m, i.e. cost of vaccinating the cohort is estimated to be £75m (£56m and £19m for, respectively, administration and vaccine costs) resulting in discounted medical care savings of £4m over their lifetime. The additional cost per life-year gained of vaccination is therefore

estimated to be £113,231 under base case assumptions. The equivalent cost per QALY gained is estimated to be £59,945.

9.4.3 Sensitivity and scenario analyses

Univariate sensitivity and scenario analyses were performed to assess the sensitivity of the results to changes in the model parameters and assumptions (Table 9.8).

Table 9.8 – Univariate sensitivity analysis - Cost per LY/QALY gained of pneumococcal conjugate vaccine programme.

	Cost per LY gained	Cost per QALY gained
Base case	**£113,231**	**£59,945**
High incidence	**£48,257**	**£23,800**
- High IPD incidence	£54,066	£31,473
- High Pneumonia incidence	£96,960	£54,757
- High AOM incidence	£109,994	£41,186
- Incidence in <1 yr. stratified in 0-6 and 6-11 mths	£111,491	£59,482
High Case-Fatality Ratio (CFR)	**£90,585**	**£52,938**
- Among IPD cases	£96,935	£55,046
- Among pneumonia hospitalisations	£104,661	£57,454
Herd immunity[a]	**£5,297**	**£5,013**
- Proportion of pnc pneumonia = 24%	£8,597	£7,899
- Proportion of pnc AOM = 15%	£5,297	£5,013
- HI effect only on IPD	£22,795	£18,622
Herd immunity[a] & serotype replacement[b]	**£30,093**	**£26,683**
Vaccine Parameters		
Duration of protection (5 years)	£123,916	£68,169
Duration of protection (15 years)	£104,859	£54,043
Cost per dose (£20)	£83,266	£44,081
Cost per dose (£40)	£143,197	£75,809
Vaccine efficacy against AOM=0%	£115,542	£83,639
Cost of a Meningitis Case		
Increased by 50%	£112,523	£59,570
Increased by 100%	£111,815	£59,195
Alternative Schedules		
3 doses, protects from 6 months	£130,071	£66,419
2 doses protects form 6 months	£84,335	£43,065
1 dose, protects from 1 year	£70,699	£31,021
Discount Rate		
Benefits 3%, costs 3%	£174,665	£81,594
Benefits 6%, costs 6%	£324,847	£120,938
Benefits 0%, costs 3%	£65,154	£38,818
Benefits 1.5%, costs 6%	£113,608	£60,144

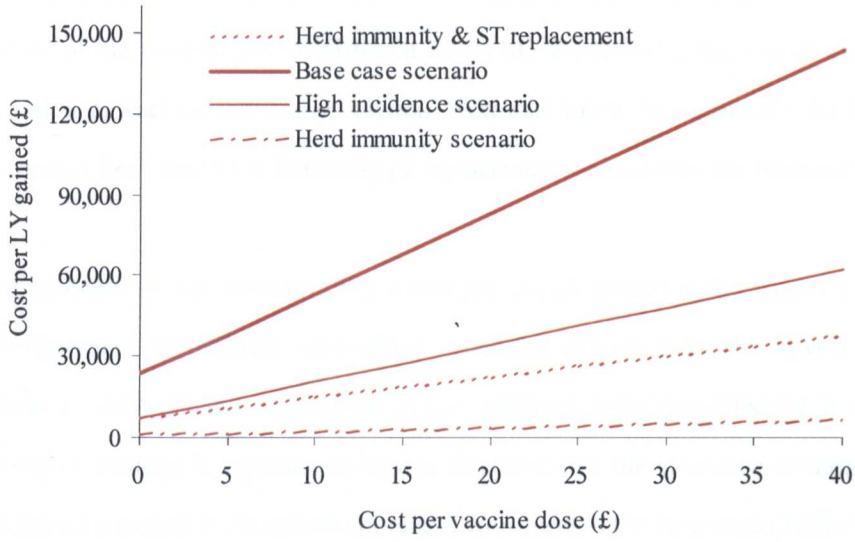
[a]Herd immunity as in Whitney and colleagues (2003); [b]complete serotype replacement (100%)

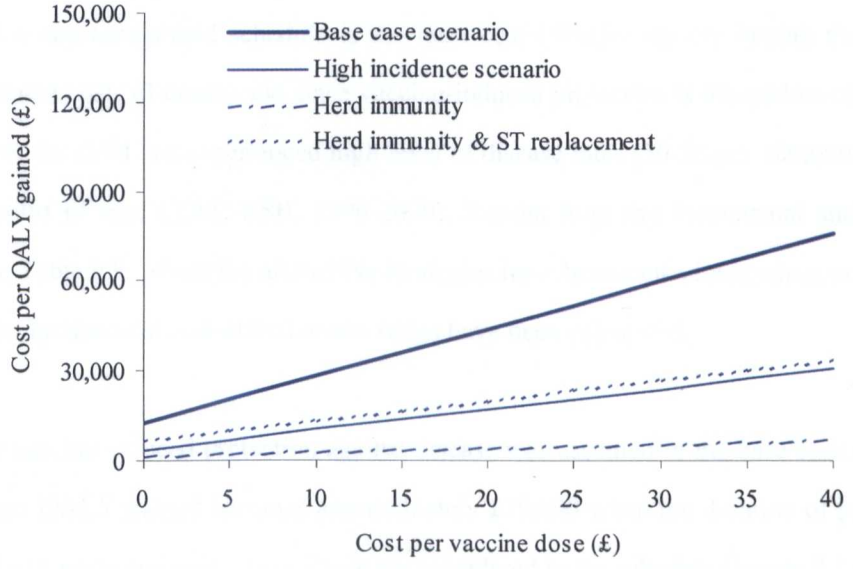
This showed that the most striking changes in the cost per life year or QALY gained occurred when the upper estimates of the incidence of IPD were used as well as when herd immunity effects were included in the model. The vaccine price is also an influential variable. If the vaccine were not reducing the incidence of acute otitis media (VE=0% rather than 7% as in the base case analysis), then the cost per QALY gained would increase substantially (£83,639 vs. £59,945 of the base case), whereas the impact on the cost per life-year gained would be negligible as the number of years gained from vaccination would be zero (no mortality is assumed due to AOM).

Figure 9.1 shows the estimated cost per life-year and QALY gained for different costs of a vaccine dose. At a maximum willingness to pay for a QALY gained of £30,000 (Devlin & Parkin, 2003), the price of the vaccine would have to be reduced to a third of its current value (under base-case assumptions). Under the high-incidence scenario, and with all other parameters at their base case values, the cost per life year gained drops to £48,257 and cost per QALY gained to £23,800.

The cost per life-year and QALYs gained decreased dramatically if indirect protection in older age groups from the introduction of infant vaccination was included. Using the levels of indirect protection reported by Whitney and colleagues (2003) for IPD and applying them to all relevant outcomes, this indirect effect alone is estimated to result in a reduction of almost 46,000 GP visits, 4,800 hospital admissions and 1,551 deaths (204 bacteraemia, 6 meningitis, 1341 pneumonias), the majority of which falls in 65+ years of age (respectively 79%, 67%, 96%). This generates an additional 12,814 life-years gained (10,319 from pneumonia cases) and 13,017 QALY gained, giving an overall cost per QALY gained of £5,013. In case herd immunity effects were only applicable to IPD patients (i.e. different serotype distribution for non-IPD cases), the cost per QALY gained is higher (£18,625) though remaining below what is considered the acceptable range. Moreover, the inclusion of a complete serotype replacement mechanism (i.e. carriage of non-vaccine serotypes completely substitutes carriage of vaccine types) increases substantially the cost per LY and QALY gained though remaining around £30,000. Note that this last scenario is significantly more cost-effective than the base case (Table 9.8, Figure 9.4).

Figure 9.1 - Sensitivity analysis - Cost per LY/QALY gained for different cost per dose of the vaccine.





Herd immunity effect assumed as in Whitney and colleagues (2003). Complete serotype replacement effect is considered (100%).

9.4.4 Alternative schedules

Figure 9.2 and Figure 9.3 show the effect of adopting different schedules on the cost per QALY gained of the programme for different levels of, respectively, the cost of the vaccine and the duration of vaccine-induced protection. Note that these results are for the base case model and neither herd immunity nor serotype replacement mechanisms are included here.

At the base case cost of the vaccine (£30), a cost per QALY gained in the range of £31,000-£66,000 is observed for different vaccination schedules (Figure 9.2); the lowest estimate resulting from a 1 dose schedule at one year of age. Although more cost-effective, it should be noted that such a strategy is expected to be less effective than the base-case resulting in 714 discounted QALYs gained in the cohort compared with 1188 in the base-case (Table 9.9). The long-term effects of such a strategy should be carefully evaluated (Chapter 8). As expected, 3 doses and a non-accelerated schedule is the least cost-effective option, having the highest vaccine related costs (3 doses) and since vaccine-induced protection is delayed to six months of age, after the child has experienced high level of disease rates (30-55 per 100,000 per year in 0-6 months of age, CDSC-RSIL 1996-2000). Results from the incremental analysis are reported in Table 9.9, where the alternative strategies have been ranked according to their net cost and the incremental cost-effectiveness ratios have been calculated.

A 10-year vaccine induced protection against disease was assumed in the base case analysis. The cost per QALY gained becomes approximately £79,000 when the duration of protection is reduced to 4 years and when three doses are considered in the schedule (Figure 9.3). For the 1 and 2 doses schedules the cost per QALY gained increases by, respectively, £10,500 and £8,400 from their base case values (£41,585 and £51,466).

Figure 9.2 - Cost per QALY gained for different vaccination schedules and varying the cost of the vaccine.

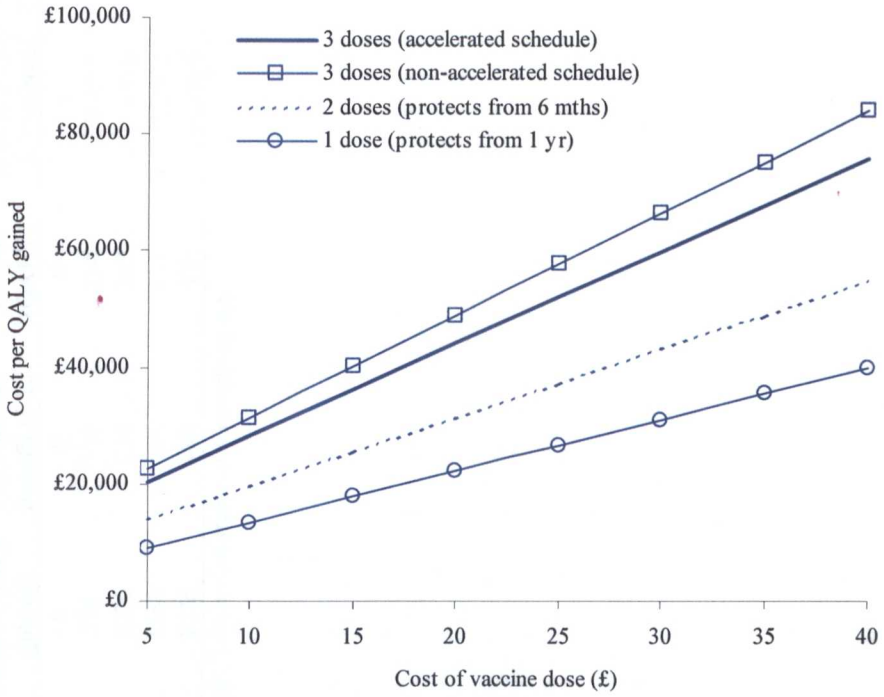


Figure 9.3 - Cost per QALY gained for different vaccination schedules and varying the duration of vaccine-induced protection.

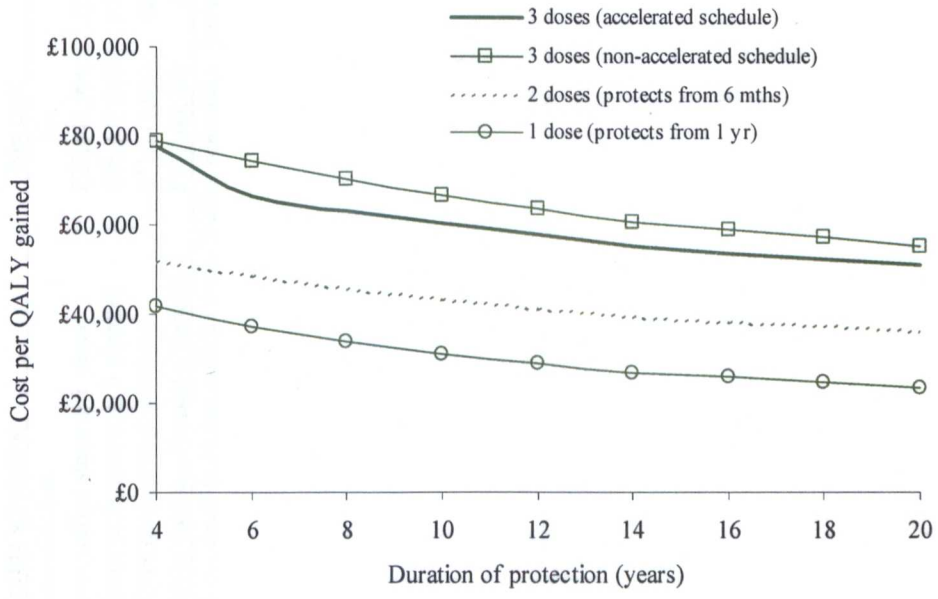


Table 9.9 - Incremental costs and benefits of alternative strategies, ranked by net cost

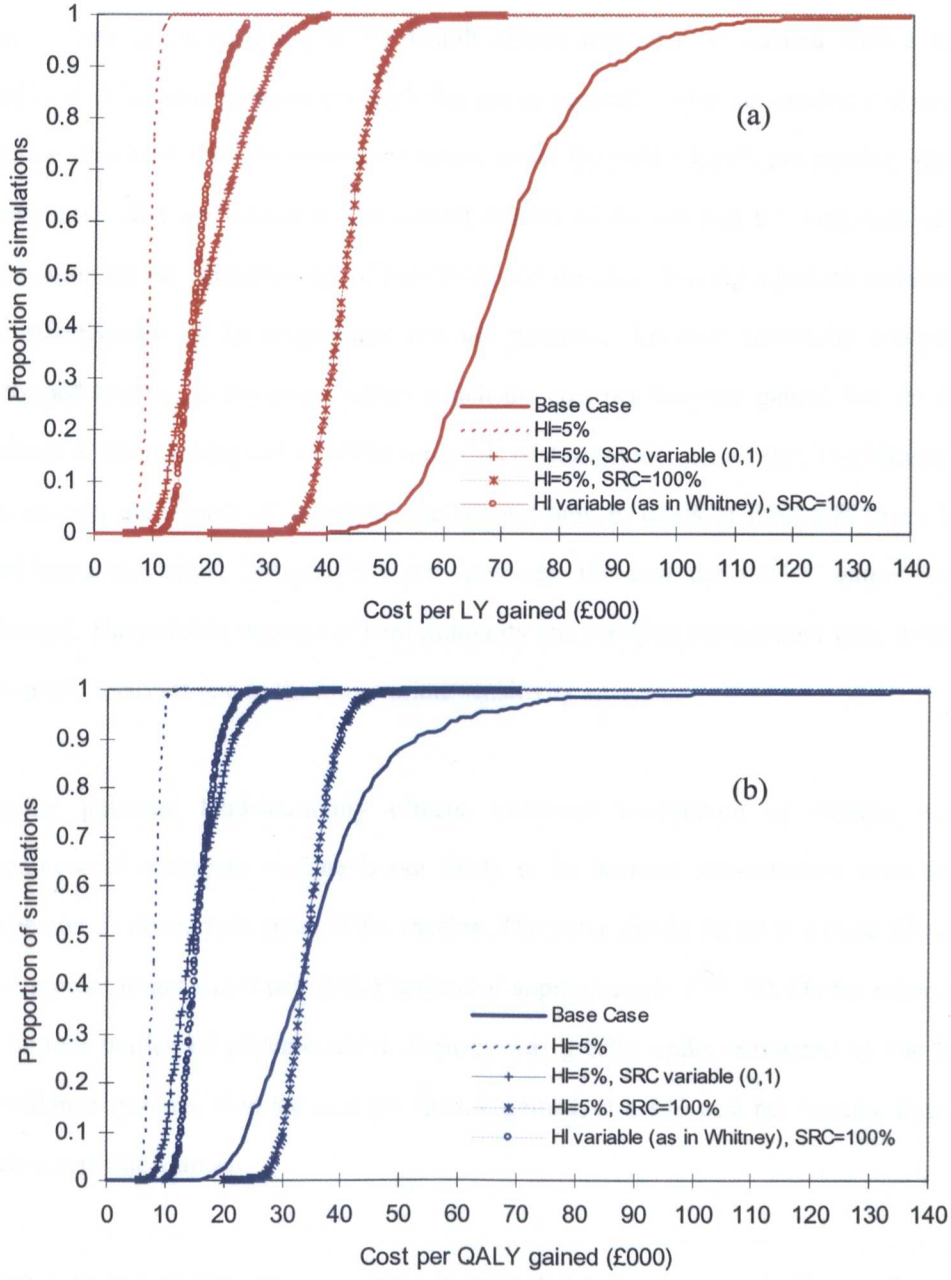
Vaccine schedules	Net cost	Incremental cost	Benefit (LY gained)	Benefit (QALY gained)	Incremental Benefit (LY)	Incremental Benefit (QALY)	Cost:benefit ratio (cost per LY gained)	Cost:benefit ratio (cost per QALY gained)
No vaccination	£0	£0	0	0	0	0	-	-
1 dose (effect starts at 1 year)	£22,141,996	£22,141,996	313	714	313	714	£70,699	£31,021
2 doses (effect starts at 6 months)	£46,333,060	£24,191,064	549	1076	236	362	£102,416	£66,802
3 doses (accelerated schedule)	£71,211,084	£24,878,024	629	1188	80	112	£312,902	£222,031
3 doses (non accelerated schedule)	£71,460,260	£249,176	549	1076	-80	-112	dominted	dominated

[a]VE assumed to be the same as in the 3-dose schedules; [b]protection starts at 3 months of age; [c]protection starts at 6 months of age

9.4.5 Multivariate sensitivity analysis

In the multivariate analysis (Figure 9.4) the impact of different herd immunity and serotype replacement scenarios is explored, keeping the discount rates fixed at their base case values (3.5% and 1.5%) and allowing the other parameters of the model to change within their specified ranges. In the base case (no herd immunity and no serotype replacement) 29% of the model simulations resulted in a cost per QALY gained of less than £30,000. When assuming a 5% reduction of Pnc disease incidence among unvaccinated individuals (herd immunity) then 100% of the model simulations are below this level (Figure 9.4b, extreme left curve) unless non-vaccine serotypes completely substitute vaccine types (serotype replacement), under which circumstances almost all simulations result in a cost per QALY gained above £30,000. If much higher levels of herd immunity were assumed, such as the ones estimated by Whitney and colleagues (2003), the reduction in disease incidence would be so dramatic that even a complete serotype replacement effect could unlikely change the cost-effectiveness of the programme. When a less strong hypothesis is assumed for serotype replacement (i.e. the level of serotype replacement is uncertain and thus is assumed to vary between 0 and 1) (see Chapter 8) and the level of herd immunity is fixed at 5%, then around 90% of the simulations are deemed to be cost-effective at an upper limit of £30,000 per LY/QALY gained. The programme is not cost-effective when looking at the cost per LY gained under base case assumptions and also when the hypothesis of complete serotype replacement is assumed (in both cases the proportion of simulations that fall above £30,000 is 100%). However, when serotype replacement varies between 0 and 1 or when herd immunity effects are as high as the ones recently published (Whitney *et al.*, 2003), then the cost per LY gained is below £30,000 in, respectively, 85% and 100% of the simulations.

Figure 9.4 - Cost per LY/QALY gained estimated from multivariate sensitivity analysis.



Base case scenario is compared to alternative scenarios that include herd immunity (HI) effect = 5% (-----), HI = 5% together with serotype replacement coefficient (SRC) =100% (xxx), HI = 5% and SRC that varies between 0% and 100% (+++), HI as in Whitney and SRC=100% (circles).

9.5 Discussion

This chapter considers the possible health effects and costs associated with a universal childhood vaccination programme with the pneumococcal conjugate vaccine and establishes baseline information on its cost-effectiveness under the public health perspective. Due to the uncertainties that are related to the current burden of disease and the long-term effects of vaccination on the epidemiology of pneumococcal disease, deriving a precise estimate of the cost-effectiveness of the programme was not possible. However, sensitivity analyses were performed looking at the range within which the cost per life-year gained lies for different prices of a vaccine dose and for different levels of disease incidence rates. In addition, to take into account the impact of conjugate vaccine not only in terms of life-years saved but also considering the effect of morbidity on survivors, the cost per QALY gained was also estimated. The possible impacts of herd immunity and serotype replacement were investigated as scenario analyses and in the multivariate sensitivity analysis.

Ignoring potential herd-immunity effects, universal vaccination of children with the pneumococcal conjugate vaccine is not likely to be deemed cost-effective from the NHS perspective at the current price of the vaccine. The latter should be set at around £10-£15 per dose in order to get a cost per QALY gained of approximately £30,000. On the other hand, if the current burden of pneumococcal diseases was greatly under estimated by the national surveillance systems, then the cost per QALY gained, at a £30 cost per vaccine dose, could reach acceptable values.

A two-dose non-accelerated programme is estimated to be more cost-effective than a three dose accelerated programme, assuming both result in similar vaccine efficacy. Nevertheless, at the current price of the vaccine, this is still not within the generally accepted threshold unless herd immunity effects occur without significant serotype replacement.

From the univariate sensitivity analysis the model estimated that the infant vaccination is highly likely to be cost-effective if the levels of indirect protection observed by Whitney and

colleagues (2003) are attributable to the vaccine and apply equally for each subsequent vaccinated cohort. Rates of pneumococcal disease are very high in the elderly (Chapter 3) and the consequent reduction of the number of cases in these age groups, without additional costs, has a large effect on the overall cost-effectiveness of the programme. It should be stressed, however, that these reductions are based on an ecological analysis of the reduction in reported IPD incidence in the US just after the introduction of the vaccine compared with the period just before (1998-99). These observed reductions should be set in the context that the incidence of IPD was falling before the introduction of the vaccine in all of these age groups, and so may partly or in whole be due to other factors. Finally, the reduction observed immediately after the introduction of the vaccine may not reflect the long-term reduction in incidence as a honeymoon period may occur (though this was not observed in the model results presented in Chapter 8). Thus, taken together, the level of indirect protection reported by Whitney and colleagues (2003) may well be an overestimate, hence in the multivariate analysis the effect of having a lower indirect protection of the vaccine (5%) among unvaccinated individuals is also investigated. However, even at this lower level of indirect protection, infant vaccination is still highly likely to be cost-effectiveness unless there is complete serotype replacement.

Serotype replacement has already been shown to occur in both pneumococcal carriage studies (Obaro *et al.*, 1996a;Mbelle *et al.*, 1999;Dagan *et al.*, 2002) and disease (Eskola *et al.*, 2001;Veenhoven *et al.*, 2003;Kaplan *et al.*, 2004) following vaccine introduction. The effect of a change in the serotype distribution on the economic analyses of pneumococcal vaccination is to reduce the effectiveness of the programme over time and, consequently, increase the cost per LY and QALY gained. Whether this increase will change conclusions on the overall economic evaluation of the programme (making it not cost-effective) still remains an open question, as little information is available on the magnitude of the herd immunity effect and on the invasiveness of the non-vaccine serotypes. From this analysis, the overall effect depends firstly on the level of indirect protection conferred to unvaccinated individuals by the vaccination programme. Moreover, it also depends on whether the new types will completely substitute those which have been eliminated by the introduction of the vaccine (in

which case the programme is not likely to be cost-effective) or else if this substitution will only be partial and, in other words, carriage of pneumococci (any serotype) will be reduced as a consequence of the introduction of the vaccine. In this latter case, although serotype replacement would increase the cost per LY/QALY gained in respect to the situation in which only herd effects were present, infant vaccination would be deemed cost-effective under most circumstances. Our conclusions on serotype replacement rely heavily on a two-strain model by Lipstich (1997;1999) that is similar to the VT and NVT model presented in Chapter 8. The models show that carriage of the non-vaccine type increases up to the level (but not beyond) that of the original vaccine-type. However, it should be noted that Lipsitch also suggests that with more than two strains it is possible to increase the prevalence of carriage over the pre-vaccination level and in the model presented in Chapter 8 this was possible if strong competition between VT and NVT was present. This possibility was not explored here and, therefore, the estimates of the negative effect of serotype replacement may be somewhat underestimated.

Currently a higher proportion of vaccine types have decreased susceptibility to antibiotics than non-vaccine types. Hence widespread immunisation should lead to a reduction in the circulation of resistant organisms (at least in the short term). If current trends continue, then the future prevalence of non-susceptible types is likely to increase and therefore the average costs of treating pneumococcal cases will also rise. This knock-on effect would render pneumococcal vaccination more attractive economically than is apparent in this analysis.

In summary, the base-case analysis (excluding indirect effects) suggests that the use of the pneumococcal conjugate vaccine in infants is not likely to be justified economically at current vaccine prices. However, this conclusion is very sensitive to assumptions regarding the current burden of pneumococcal disease and the future impact that vaccination will have in the unvaccinated, and on the future serotype distribution. Herd immunity, even with a partial serotype replacement, is likely to render infant vaccination cost-effective. This is the first analysis to quantify the impact of these indirect effects on the cost-effectiveness of pneumococcal conjugate vaccination.

CHAPTER 10 - DISCUSSION

10.1 Introduction

This thesis develops a variety of methods to further the understanding of the epidemiology of pneumococcal disease and carriage and to prepare the necessary ground for investigating the impact of alternative vaccination strategies. These methods range from direct observation and analysis of surveillance data, through more complicated statistical and mathematical models to economic evaluation. Novel statistical techniques have provided parameter estimates and deepened the understanding of basic biological concepts of pneumococcal carriage and transmission. The short and long-term effects of vaccination on pneumococcal carriage have been investigated through mathematical modelling. Moreover, economic evaluations have been utilised to assess the cost-effectiveness of the alternative vaccination programmes with the available pneumococcal vaccines.

10.2 Overview

Although polysaccharide pneumococcal vaccines have been available for decades and recommended to certain at-risk groups, the level of protection that the vaccine confers to these subgroups has been debated and, moreover, disease incidence rates in very young children have not been affected due to the poor immunogenicity of these vaccines in the first two years of life. Following the Hib and MenC experiences, pneumococcal conjugate vaccines were developed and a 7-valent formulation of the vaccine (Prevenar@ Wyeth) has been recommended since January 2002 in England and Wales for children less than 2 (recently extended to 5) years of age, who are at special risk of pneumococcal infection. The

vaccine not only appears to offer some protection against invasive and non-invasive pneumococcal disease (Eskola *et al.*, 2001;Black *et al.*, 2002;Black & Shinefield, 2002;Kaplan *et al.*, 2004), but substantial evidence is now available on the protection it confers against pneumococcal colonisation (Dagan *et al.*, 1996a;Mbelle *et al.*, 1999;Dagan *et al.*, 2002;Yeh *et al.*, 2003). Though this has important positive public health implications as it generates a reduction of pneumococci circulating in the population and, consequently, a reduction of pneumococcal disease incidence rates also among unvaccinated individuals (herd immunity), it also raises a number of questions on the long terms effects of the vaccine on both pneumococcal carriage and disease (Chapter 2). Several studies have shown an increase of carriage of non-vaccine serotypes among vaccinated and unvaccinated individuals (serotype replacement) as well as an increase in otitis media and invasive disease caused by these serotypes. Nevertheless, due to the considerable burden of pneumococcal disease, the severity of some of its conditions and the risk of disabling sequelae in very young children (Chapter 3), widespread vaccination with the pneumococcal conjugate vaccine is now under consideration at the Department of Health and discussions are ongoing on whether to incorporate PCV in the routine immunisation schedule.

10.3 Surveillance

The importance of surveillance systems to understand the epidemiology of pneumococcal infection and to monitor trends in the pre widespread vaccination era was demonstrated. Although a number of data sources are available for pneumococcal disease, surveillance has particularly relied upon laboratory notifications, since this is the most specific source of information on severe infections and reports on the serogroups and other characteristics of the pathogenic serotype (i.e. antimicrobial resistance). This information is particularly important when a vaccine programme does not target all the circulating types. While this provides a solid base for disease surveillance, enabling trends to be detected in a timely manner, it is clear that laboratory reports underestimate the real incidence of pneumococcal disease, as they exclusively record invasive infections which only represent the tip of the iceberg of all pneumococcal related conditions. It is important to assess the true burden of disease when

considering the impact, particularly, the economic impact of public health intervention programmes. Hospital admissions data (HES) and Royal College of General Practitioner data (RCGP) were both shown to be valuable sources of information for retrospective analysis of less severe pneumococcal conditions (pneumonia and otitis media). Moreover HES data also provided interesting insights on co-morbidities related to pneumococcal hospitalisations, and the assessment of the burden of disease among patients at high and low risk of infection (Chapter 3). This information was used in the cost-effectiveness analysis of the polysaccharide vaccine (Chapter 5).

10.4 Infection vs. Disease

Pneumococcal disease is, however, a rare outcome of infection with *S.pneumoniae* and most infected individuals will become asymptomatic carriers. Understanding the role of carriage in pneumococcal transmission was therefore crucial in order to assess the impact of vaccination programmes with the conjugate vaccine (which also protects against colonisation). Data from a longitudinal study of pneumococcal carriage in UK households were analysed and a novel modelling framework was developed in order to estimate age-specific transmission parameters and the duration of carriage and hence evaluate the importance of household versus community acquisition of the organism (Chapter 6). Longitudinal datasets can be very useful in deepening the understanding of a pathogen's dynamics within the human host and in highlighting the individual characteristics that can affect the transmission dynamics of the infectious agent. However, different levels of complexities (clustered data and unobserved events) are embedded in this type of data and, thus, non-straightforward techniques have to be adopted to extrapolate some insights about the organism characteristics. In the past, complex statistical methods have been utilised to address these difficulties and the challenges posed by longitudinal studies (Auranen *et al.*, 2000). These methods consisted of data augmentation (to deal with the unobserved events) and MCMC simulations to derive the posterior distributions of the model parameters. Though this approach certainly represents a valuable technique, being flexible and providing measures of the variability of the parameter estimates, on the other hand it is much more complex and computationally intensive. Conversely, the model we

developed here though has certainly some limitations in terms of flexibility and possibility to add, for example, additional statuses (i.e. immunity), it provided parameter estimates which fitted well the observed pattern and it allowed individual characteristics to be included in the analysis and their relationship to carriage acquisition to be investigated.

10.5 Serotype diversity

The pneumococcus is a very diverse pathogen and more than 90 distinctive serotypes circulate in the population. Though it is known that differences exist among them in terms of duration of carriage and invasiveness (Smith *et al.*, 1993;Brueggemann *et al.*, 2003), precise estimates of their transmission parameters have never been derived and neither have inferences of their interfering transmission behaviours. The observed changes in the circulating serotypes after the use of conjugate vaccines (serotype replacement) represent a signal that serotypes are indeed competing to gain access within the available hosts, and that disturbing this system by introducing widespread vaccination may have positive or negative effects depending on the relative invasiveness of the new types and the immunological response of the host. Serotype replacement and the analysis of the dynamics of competing serotypes is certainly a central issue not only for *S.pneumoniae* infection, but also for a number of other antigenically diverse pathogens (e.g Group A Streptococcus, Human Papillomavirus) for which vaccines are under development (McMillan *et al.*, 2004;Batzloff *et al.*, 2004;Ault *et al.*, 2004). The use of vaccines designed to protect against certain variants of these organisms may inadvertently lead to increases in the prevalence of non-targeted variants of the same pathogen. This serotype replacement, a consequence of direct and indirect competition between the variants, has the potential to result in adverse as well as beneficial public health effects. To explore the differences and interaction between pneumococcal serotypes, the model presented in Chapter 6 was further extended to include serotype specific information that was available from the same longitudinal study in UK families (Chapter 7). Five serotypes were considered and great dissimilarities were estimated among them in terms of both transmissibility and duration of carriage. Whereas for some of the serotypes the relationship decreasing duration of carriage with increasing age was still valid, for others the

opposite was true. Interestingly, for each of the five serotypes the community acquisition rate was significantly higher in children than in older family members, which shows that children are more likely to be the source of infection in the household. The existence of competition among the serotypes was also assessed, estimating the relative risk of acquiring one serotype if already colonised by another one as opposed to a non-carrier. Though this is certainly a crude simplification of the competing forces of the over 90 different circulating serotypes, it allowed one to scratch the surface and to explore the diversity of the organism and the distinctive behaviour of each of the target serotypes.

10.6 Transmission Dynamics

A transmission dynamic model was developed using parameter estimates from Chapter 6 to investigate the impact of different vaccination programmes that may be implemented if the vaccine will be introduced in England and Wales (Chapter 8). This allowed the transmission dynamics of the organism as well as the long-term effects of vaccination on carriage of VT and NVT pneumococci to be explored. This type of model has been extensively used in the past to assess the transmission dynamics of infectious agents and the positive and negative impacts any intervention programme may have on the endemic equilibrium of the organism in the population (Babad *et al.*, 1995;Brisson *et al.*, 2002). Moreover, outcomes from these models have provided potential post-vaccine disease incidence rates, on which to base cost-effectiveness analysis of alternative intervention strategies. Chapter 8 of this thesis covered only the initial stages of this task as it explored the effects of vaccination on the prevalence of VT and NVT carriage rather than disease incidence rates. The results presented here, however, provided further insights into the organism dynamics and on the uncertainty in regards to certain parameter estimates. The contribution of various elements of vaccination programmes was assessed and the effect of different levels of competition between vaccine and non-vaccine serotypes on the outcome of the vaccination programme was shown. Future work will clearly build on this model structure.

10.7 Cost Effectiveness of Vaccination

Increasingly new medical interventions, including vaccination programmes, must be justified by economic analyses. This provides public health professionals with summary measures that should then influence policy decisions. Performing an economic analysis of a vaccination programme, in particular, ideally requires the consideration of any short, middle and long-term effect of the vaccine. Whereas short-term effects can be easily derived, given possible coverage rates and the protection afforded by the vaccine, longer ones are much more difficult to estimate and also to incorporate in the economic assessment. Moreover, we have seen in this work (Chapter 5) that several possible analyses can be performed and that the decision of which economic approach to use may also influence the outcome. Cost-effectiveness analyses of pneumococcal vaccines (PPV and PCV) were performed in Chapters 5 and 9 of this thesis. To assess the cost-effectiveness of PPV, estimates of the level of protection conferred by the vaccine to high risk as well as healthy elderly were derived performing a meta-analysis of the available randomised and quasi-randomised controlled trials (Chapter 4). The vaccine appeared to offer no protection against pneumococcal pneumonia, little protection against IPD among the high-risk elderly whereas some protection among the healthy elderly. Though these estimates lacked of statistical significance and this analysis was limited by the paucity of the data and the weaknesses of the studies included, they provided insights not only on the difference between these two risk groups, but also on the levels of uncertainty that are present for these estimates and that was then incorporated in the cost-effectiveness analysis of Chapter 5. The latter was performed developing a cohort static model that showed that vaccinating all elderly individuals (rather than only high-risk ones) would result in the most cost-effective option with the cost per life-year gained well within what is currently considered the acceptable range for the UK. A similar cohort model was developed to assess the cost-effectiveness of the conjugate vaccine in children (Chapter 9) adopting the different vaccination strategies that are currently under discussion at the Department of Health. Herd immunity and serotype replacement, both key elements to consider if wanting to assess the middle and longer-term effect of any vaccination programme (Chapter 8), were included in

the model and showed that cost-effectiveness results were highly sensitive to their values. Though serotype replacement may in fact partially counterbalance the positive effects of herd immunity, the final outcome of any vaccine intervention is dependent on the real magnitude of these indirect effects, the time it takes for them to occur in the population and, not least, the characteristics of the non-target serotypes. As most of these are still unknown, different scenarios were investigated in this thesis, which will be revised as soon as more information becomes available and the results of the more comprehensive transmission dynamic model will be generated.

10.8 Future work

There are two major issues that will be addressed in the future as continuation of this work. The first one relates to the cost-effectiveness of the conjugate vaccine. The analysis presented in Chapter 9, which was based on a static cohort model, did not adequately account for herd immunity effects, since it assumed constant forces of infection, rather than varying them according to the number of infectious individuals in the population. The transmission dynamic model described in Chapter 8 will be further developed to include pneumococcal disease (invasive and non invasive) and changes in disease incidence rates, as a consequence of vaccination, will be estimated. The cost-effectiveness of PCV will be re-analysed using this model as the basis for predicting the future incidence of disease under a range of vaccine strategies.

Secondly, Chapters 6-8 are based on the assumption that pneumococcal transmission can be described with an SIS model structure, i.e. no immunity after carriage. This was a necessary simplification of the real host-pathogen interaction required to make progress, and it allowed a deeper understanding of pneumococcal transmission and also some inference on the competition between the most prevalent types. However, it remains to be seen to what extent this assumption is true and the influence that immunity to reinfection has on transmission dynamics. The considerable antigenic diversity presented by *S.pneumoniae* suggests that immunity is an important evolutionary force for the pathogen. On the other hand, the

heterogeneity itself might mean that the SIS framework is adequate to describe the hosts' experience. These issues can be explored using an individual based model including partial and temporary immunity. The advantage of this approach is that models can be developed which include personal characteristics (important for pneumococcal carriage), serotype information (when carriage is detected) as well as family-related behaviours (i.e. day-care attendance). This model could be fitted to the longitudinal carriage data and investigations on the serotype-specific immunity and cross immunity after a carriage episode could be performed.

10.9 Conclusion

S.pneumoniae causes a substantial burden of disease worldwide. Epidemiology, mathematical modelling and economics are tools that together can help in gaining a better understanding of the organism behaviour and on the host-pathogen interaction that is essential for evaluating the impact of any vaccination policy. Though more work is clearly needed in order to proceed in the understanding of these relationships, this thesis has posed the basis for the current discussion and has furthered the understanding of the transmission patterns of the organism. Moreover, the modelling framework developed in this work represents a robust method that can be used for investigating any other longitudinal dataset of infectious diseases and to infer intrinsic transmission characteristics of the organism. Also it could be adapted to look at other antigenically diverse pathogens for which vaccines are currently under development. This latter point represents a challenge that ought to be addressed considering that public health interventions should increasingly be based on solid ground and that longer terms effects will necessarily have to be included in the economic evaluation.

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APPENDIX 1 – REPRINTS OF PUBLISHED PAPERS

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INFECTIOUS DISEASES

The 23-valent pneumococcal polysaccharide vaccine. Part I. Efficacy of PPV in the elderly: A comparison of meta-analyses

Alessia Melegaro[1,2] & W. John Edmunds[1,3]

[1]*Modelling and Economics Unit, HPA Communicable Disease Surveillance Centre, London;* [2]*Department of Biological Sciences, University of Warwick, Coventry;* [3]*Department of Economics, City University, London, UK*

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Abstract. A 23-valent polysaccharide pneumococcal vaccine (PPV) has been available in the UK for more than 20 years and is currently recommended for use in high-risk groups (HRG) of 2+ years of age. The degree of protection afforded by the PPV remains a critical issue, although a number of randomised clinical trials and case–control studies (CCS) have been published. The aim of this work is to review the estimates on the efficacy of PPV against pneumococcal pneumonia and invasive pneumococcal disease (IPD) in the elderly and to perform a meta-analysis in order to obtain a pooled estimate of the level of protection in high and low risk individuals. These two groups of individuals are at the centre of the current debate on whether or not to extend the vaccination programme to all elderly individuals 65+. Only randomised and quasi-randomised studies are included in the analysis and results are compared with previous meta-analyses. The effect of the inclusion of observational studies is investigated in the sensitivity analysis. When taken with the results of other meta-analyses and observational studies, it appears that PPV offers protection against IPD in the general elderly population (VE = 65%; 95% CI: −49–92%) whereas it has a moderate effect in the high-risk elderly (VE = 20%; 95% CI: −188–78%). The vaccine has little or no effect against pneumonia (VE = 16% in the general elderly and −20% in HRG).

Key words: Elderly, High-risk, Meta-analysis, Polysaccharide pneumococcal vaccine (PPV), Vaccine efficacy (VE)

Abbreviations: CCS = case–control studies; HRG = high-risk group; IPD = invasive pneumococcal disease; OR = odds ratio; PPV = polysaccharide pneumococcal vaccine; RCT = randomised controlled trial; VE = vaccine efficacy

Introduction

Streptococcus pneumoniae is an important bacterial agent of the respiratory tract, which can cause serious disease mainly in children and in the elderly. The main reservoir is the nasopharynx and the possible outcomes, once colonisation has taken place, are the clearance of the organism, the asymptomatic persistence for several months (carrier state), or the progression to disease. During disease, the bacteria can either spread to adjacent mucosal tissues, causing mucosal infection (otitis, sinusitis, and pneumonia) [1, 2], or else invade the bloodstream, or other sterile sites, producing an invasive condition (bacteraemia, septicaemia and meningitis) [3].

A 23-valent-polysaccharide pneumococcal vaccine (PPV) has been available in the UK since the early 1980s and is currently recommended for use in high-risk individuals of 2+ years of age [4]. These include persons with asplenia or severe dysfunction of the spleen, chronic renal disease, immunodeficiency, chronic heart, lung, or liver diseases, and diabetes mellitus. The degree of protection afforded by the PPV remains an issue of some debate despite the existence of a number of randomised (or quasi-randomised) clinical trials, case–control and indirect cohort studies. These studies have attempted to investigate the vaccine efficacy (VE) against pneumococcal pneumonia and/or invasive pneumococcal disease (IPD). A number of meta-analyses have also been used to obtain overall pooled estimates of VE, because of the lack of power of the single trials to detect a significant effect of the vaccine.

The purpose of this work is to review estimates on the efficacy of the polysaccharide vaccine against invasive and non-invasive pneumococcal disease, and to perform a meta-analysis in order to obtain estimates of protection for, respectively, the general elderly population and elderly at high-risk of disease. Although, in fact, four other meta-analyses have been published to assess the efficacy of PPV in adult populations [5–8], none of these focused exclusively

on elderly patients and, in particular, none differentiated between the general elderly and elderly at a higher risk of infection. The level of protection of the vaccine in these groups represents a crucial aspect in the current debate on whether or not to extend the vaccination programme to all elderly individuals. For these reasons and because the vaccine is not likely to be recommended in healthy young adults, where the incidence is low, the analysis will concentrate only on randomised and quasi-randomised[1] clinical trials that were performed among elderly populations. Moreover, there is evidence that the VE may be lower in the elderly [9].

Methods

Inclusion criteria and information collected from the eligible trials

A Medline and a PubMed literature search were used to identify published studies on PPV efficacy, without any year or language restriction and using the following keywords to identify relevant articles: 'Pneumococc*', 'vaccination', 'pneumococcal vaccine', 'immunisation' and 'clinical trial'. Papers that were including in the title words such as 'children', 'infants', 'conjugate', 'carriage' and 'otitis media', were excluded from the list of selected papers. Previous meta-analysis and reviews were also extracted and checks were made in order to have a complete list of studies. References of the retrieved papers were also examined. The inclusion criteria that were adopted to select the papers to be part of the analysis were: (1) All randomised and quasi-randomised controlled trials with a well-defined randomisation or quasi-randomisation process and with a PPV and a control group (placebo or a control vaccine); (2) targeted immunocompetent and immunocompromised elderly individuals (50+ years of age) and (3) assessing at least one of the following endpoints: Pneumococcal pneumonia and/or IPD. The definition of pneumococcal pneumonia that was used consisted of a clinically and radiographically confirmed diagnosis of pneumonia, with *S. pneumoniae* cultured from sputum or a nasal swab. Diagnoses made on the basis of a twofold rise in pneumolysin antibody level in paired serum samples were also accepted, due to the high sensitivity (97.8%) and specificity (83.4%) that was shown by Leinonen et al. [10] for these tests, using standard procedures (i.e. culture of blood or sputum) as reference methods. Similarly, the technique of pneumococcal antigen detection by electrophoresis of urine specimen was also accepted as a diagnostic method for pneumococcal pneumonia. IPD patients had to be defined as bacteraemic cases with *S. pneumoniae* isolated from blood or any other usually sterile body fluid (e.g. peritoneal, pleural, cerebrospinal, or joint). Although the two endpoints were not consistently assessed throughout the studies (with some studies that were including bacteraemic cases within the pneumococcal pneumonia group and some others that were considering the two groups distinctively) we decided to consider them separately in the base case analysis. Estimates of VE for pneumococcal disease (invasive and non-invasive) are given in the sensitivity analysis where the number of cases of pneumococcal pneumonia and IPD are summed up for each trial and a unique level of protection is produced.

The two authors independently read the selected papers and extracted information on study design (type of interventions, number of serotypes included in the vaccine (valency), follow-up time) and on the participants (demographic characteristics and background health conditions) of each trial. Similarly, the number of pneumococcal pneumonia and bacteraemic cases was assessed for each study and compared to that published in previous meta-analyses. The Jadad's system [11] was used by the two reviewers to score each report according to whether or not randomisation, blinding and description of withdrawals were part of the study. One point was given for each of these, and one additional point was added or subtracted when either methods of randomisation or blinding were, respectively, well described by the authors or inadequately performed. The maximum possible score was five. When discrepancies in the quality evaluation existed, the two authors met and discussed to resolve them. All the studies that were not reporting clear information about the age of the participants, about the randomisation process or the diagnostic procedures that were used were excluded from the analysis.

Information about the health conditions of all the study populations was collected and the proportion of high-risk individuals in each trial was assessed (where high-risk is defined as those categories to which the vaccine is currently recommended in the UK [4]). As most of the studies included in their analysis at least a proportion of institutionalised patients or elderly with some chronic condition, we decided to consider at high-risk those study populations that had at least 50% of the individuals with some chronic condition or immunodeficiency. When the proportion was below this threshold, then the trial was considered to be a study of the general elderly population. This criterion was widened in the sensitivity analysis where all the trials in which more than 20% of the study population was at high-risk, were included when calculating VE in high-risk groups (HRG). Case–control and indirect cohort

[1] A method of allocating participants to different forms of care that is not truly random; for example, allocation by date of birth, day of the week, medical record number, month of the year, or the order in which participants are included in the study (e.g. alternation).

studies were also included in the sensitivity analysis to assess whether their results are coherent with findings from RCT and to evaluate the effects they might have on the overall pooled estimates that were produced using randomised and quasi-randomised controlled trials for VE against IPD in high and low-risk elderly.

Statistical methods

In order to estimate summaries of the effect size (i.e. odds ratio (OR)) in different trials, several statistical techniques are available. One of the most crucial differences among them is related to whether or not they incorporate between-study variation (heterogeneity) and, consequently, to whether the model used is a fixed or a random effect model. This latter type of model, which is appropriate when significant heterogeneity is present between studies, produces a more conservative estimate (i.e. wider confidence intervals) of the pooled effect size.

Here we assume that the trials considered are a random sample from a hypothetical population of studies, and thus the DerSimonian and Laird [12] random effect model OR was adopted in the base-case. This computes a weighted average of individual studies' ORs taking into account both sampling variation and between study heterogeneity. Sensitivity analysis was performed in order to assess whether different model assumptions would have changed the results. Therefore, the Mantel–Haenszel fixed effect method was adopted under the assumption that the differences among the results of the studies were due to chance alone. Further sensitivity tests were performed modifying the inclusion criteria in the analysis and considering only RCT.

All analyses were performed using *Stata 6.0* and the results are presented using forest plots with single and overall OR and related 95% CIs. The results obtained are compared with previous meta-analyses and the definition of VE that was used is $VE = (1 - OR) \times 100$ (%) [13], with confidence intervals of the pooled estimate obtained, similarly, as a function of those derived for overall OR. ORs are good approximation of relative risks when outcomes are comparatively rare, as in the studies included in this analysis, and have desirable properties when combining results across studies [14].

Results

Literature review

Of all the studies retrieved from the literature search, six randomised and three quasi-randomised clinical trials were selected that satisfied the inclusion criteria (Table 1), although three of them [15–17] were methodologically weak according to the Jadad scores assigned by the two reviewers. Of the nine studies, five were European studies [16–20], three American [15, 21, 22], and one Canadian [23]. The study by Kaufman [15], although it is one of the largest trials, and has the largest mean effect, both for pneumonia and IPD (Table 1), was not included in our base case pooled estimates due to the methodological weaknesses that were present in the design and implementation of the study (it was an open trial, performed over a period of 6 years during which the participants were recruited using different randomisation procedures: indeed the first cohort recruited into the trial were not randomised and patients volunteered for the injection. Furthermore, it used 2 and 3-valent vaccines, and 21% of the participants were under 60 years of age). Three studies that were included in previous meta-analyses were excluded from ours due to the presence of healthy young adults in their study population [24–26] (Table 2). The mean age of the study population was available for all the trials used in our analysis (range: 61–74 years), as well as the proportion of chronically ill elderly (range: 27–100%). Four studies that were undertaken among elderly with respectively, chronic obstructive pulmonary disease (COPD), bronchogenic carcinoma, or various chronic conditions, as defined in the recommendations, were defined as studies of HRG [18, 21–23]. In addition, a Swedish study [20] was included in the HRG on the basis of the history of community-acquired pneumonia (CAP) that the study participants had experienced, and due to the high proportion of HR individuals (58%) that were present in the trial. Three studies were undertaken among elderly patients not experiencing, in high percentages, specific chronic conditions [16, 17, 19]. Their study participants were considered representative of the general elderly population, although they all reported a proportion of high-risk individuals lower than 50% but, nevertheless, in the range of 27–34% (Table 1). These studies were included when the HR threshold was lowered to 20%.

In accordance with previous meta-analyses [6–8], we decided not to include the study by Davis et al. [21] for our base case estimate of VE against IPD. Although, in fact, a case of pneumococcal bacteraemia was reported among the participants, this occurred during a terminal episode of pneumonia in a severely ill patient who had been hospitalised on a long-term basis for respiratory insufficiency, repeated urinary tract infections, cardiac failure and acute pancreatitis. The effect of this case on the estimate of VE against IPD in HRG was explored in the sensitivity analysis.

Statistical analysis

The individual trials and summarised OR (95% CI) are shown in Figures 1 and 2, for the two study outcomes and according to the different level of risk of the study participants. The overall results, when

Table 1. Randomised and quasi-randomised trials on VE against pneumococcal pneumonia (PP) and IPD

Reference	Jadad score	Study type	Type of randomisation	Study population	Mean age in years	Sample size – vacc.	Sample size – controls	PP in vaccinated (control)[a]	IPD in vaccinated (control)[a]	HRG (%)	Vaccine type	VE for PP (95% CIs/ *p*-value)	VE for IPD (95% CIs/ *p*-value)
Kaufman et al. [15]	0	QRCT– Open	Not randomised in the first 2 years Randomisation unclear in the last 4 years	Institutionalised elderly in NY City home and hospital	68.7 (79% is 60+)	5750	5153	34 (96) [H+, F–, M–, C–]	8 (34) [H+, F–, C–, M–]	No (n.a.)	2 and 3-val	69% (53–80%)	79% (54–92%)
Gaillat et al. [16]	0	QRCT– Open	Randomisation done after stratifying by the level of risk	Elderly hospitalised /nursing home patients	74 (all 55+)	937	749	3 (9) [M+, H–, C–, F–]	0 (1) [F+, H+, C+, M–]	Mix (27%)	14-val	74% (2–93%)	100% (n.s.)
Klastersky et al. [18]	3	RCT– Single blind (recipients unaware)	Vaccine in numbered boxes, prepared according to prior randomisation by vaccine manufacturer	High-risk adults and elderly with bronchogenic carcinoma	61 (all 42–78)	26	21	1 (3) [C+, M–, F+, H–]	1 (1) [F+, H+, M+, C+]	Yes (100%)	17-val	76% (–150–98%)	20% (n.s.)
Davis et al. [21]	3	RCT– Double blind	Randomisation based on a table of random numbers	High-risk elderly with COPD	63 (all 50+)	50	53	1 (0) [M–, H+, F+, C–]	n.a. [F–, C+, H+, M+]	Yes (100%)	14-val	Infinite	n.a.
Leech et al. [23]	3	RCT– Double blind	Randomisation done after stratifying by age and FEV_1[b]	High-risk elderly with COPD	67 (all 40–89)	92	97	n.a.	1 (0) [F+, M+, H+, C–]	Yes (100%)	14-val	n.a.	Infinite
Simberkoff et al. [22]	3	RCT– Double blind	Randomisation done using sequence of numbers to patients and syringes	High-risk elderly /ambulatory veteran	61.3 (82% is 55+)	1145	1150	19 (15) [H–, M+, C+, F+]	2 (1) [F+, H+, M–, C–]	Yes (100%)	14-val	–28% (–153–35%)	–101% (n.s.)
Koivula et al. [19]	3	RCT– Single blind (recipients unaware)	Randomised by computer	All the elderly inhabitants of Varkaus	69[c] (all 60+)	1364	1473	26 (33) [C–, M+, H–, F–]	n.a. [F+, C+, M+, H+]	Mix (34%)	14-val	15% (–43–50%); HRG: 56% (3–80%)	n.a.
Ortqvist et al. [20]	5	RCT– Double blind	Random numbers given by vaccine manufacturer	Middle-aged and elderly treated in hospital for CAP	69.3 (all 50–85)	339	352	19 (16) [F–, H–, M+, C+]	1 (5) [F–, C+, M+, H–]	Yes (58%)	23-val	–25% (–147–37%)	79% (–77–98%)
Honkanen et al. [17]	0	QRCT– Open	Randomisation by year of birth: odd/even	Elderly living in 35 adm. districts	73.6 (all 65+)	13980	12945	52 (40) [C–, M–, H–, F–]	2 (5) [M–, C–, H–]	Mix (31%)	23-val	–20% (–90–20%)	60% (–40–90%)

n.a. = not available.
[a] [H+(–)] = in agreement (in disagreement/not included) with Hutchinson's meta-analysis (F = Fine, M = Moore, C = Cornu).
[b] FEV_1 = forced expiratory volume in 1 second.
[c] Median age.

Table 2. Meta-analyses and studies included in the calculation of the overall OR for IPD and pneumococcal pneumonia (PP)

	Fine 1994			Hutchison 1999	Moore 2000		Cornu 2001		This study		
	All studies	LRG	HRG	All studies	Healthy	HRG	All studies	HRG	LRG[a]	HRG[b]	MIX[c]
VE against IPD	66% (52–76%)	68% (54–78%)	−23% (−449–72%)	73% (50–85%)	82% (66–91%)	47% (−94–86%)	71% (58–80%)	42% (0–82%)	65% (−49–92%)	20% (−188–78%)	44% (−45–79%)
VE against pneumococcal pneumonia	53% (37–65%)	60% (44–71%)	2% (−89–49%)	42% (28–53%)	84% (77–89%)	12% (−7–28%)	40% (4–63%)	−16% (−80–26%)	16% (−50–53%)	−20% (−92–25%)	−10% (−64–26%)
Papers											
McLeod 1945				PP							
Austrian 1976	IPD/PP	IPD/PP			IPD/PP		IPD/PP	IPD/PP			
Smit 1977					PP		PP				
Riley 1977	IPD	IPD		IPD	PP		IPD				
Austrian 1980	IPD	IPD		PP		PP	PP				
Kaufman 1947				IPD/PP							
Gaillat 1985	IPD		IPD	IPD/PP		PP	IPD	IPD	IPD/PP		IPD/PP
Klastersky 1986	IPD/PP		IPD/PP	IPD/PP		IPD/PP	IPD/PP	IPD/PP		IPD/PP	IPD/PP
Simberkoff 1986	IPD/PP		IPD/PP	IPD/PP		PP	IPD/PP	IPD/PP		IPD/PP	IPD/PP
Leech 1987	IPD		IPD	IPD		IPD		IPD		IPD	IPD
Davis 1987	IPD/PP		IPD/PP	PP				PP		PP	PP
Koivula 1997						PP		PP	PP		
Ortqvist 1998						IPD/PP	IPD/PP	IPD/PP		IPD/PP	IPD/PP
Honkanen 1999									IPD/PP		IPD/PP
French 2000						PP					

[a] Healthy elderly.
[b] Proportion of HR > 50%.
[c] Proportion of HR > 20%.

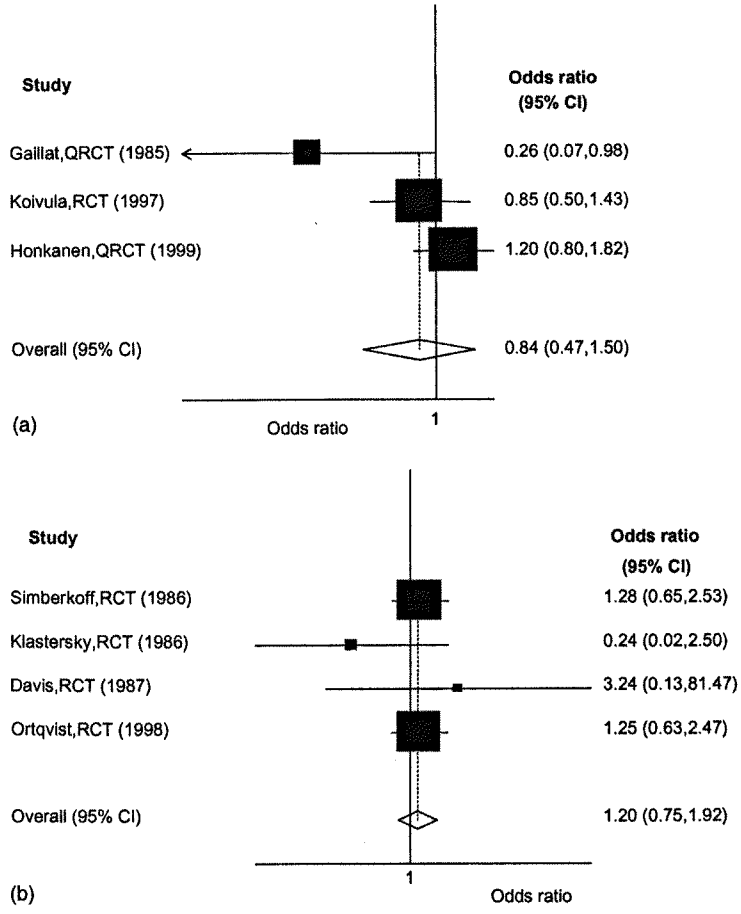

Figure 1. OR (dotted line) and associated 95% CI for pneumococcal pneumonia in (a) general elderly and (b) high-risk elderly.

RCT and case–control studies (CCS) are considered together, are presented in the sensitivity analysis.

VE against pneumococcal pneumonia

A low level of protection of the polysaccharide vaccine against pneumococcal pneumonia among elderly individuals has already been shown [17, 19, 20, 22]. Among the RCT included in the analysis, seven studies had pneumococcal pneumonia diagnosed with one of the methods outlined in the inclusion criteria. All of them showed a negative or non-significant effect against pneumococcal pneumonia in the elderly, with VE ranging from −28% (−153–35%) [22] to 76% (−150–98%) [18]. Overall pooled estimates of the OR were produced in order to assess the significance of previous findings and, most importantly, to determine the level of protection by risk group. A non-significant and very low level of protection of the vaccine was found, VE 16% (−50–53%) using a random effects model and including in the estimate the three trials [16, 17, 19] representative of the general elderly population (Figure 1a). Bacteraemic cases were excluded from the calculation. The estimated mean protective effect of vaccination is actually negative (though not significant) when considering the studies that were performed among high-risk elderly [18, 20–22], VE = −20% (−92–25%) (Figure 1b).

Comparing to previous meta-analyses, a level of protection of 60% (44–71%) and 2% (−89–49%) in, respectively, low and high-risk adults was shown by Fine et al. [5]. Their estimates of VE, which are higher than those reported here, are influenced by the inclusion of trials that were performed among healthy young adults [24–26]. Similarly, another two meta-analyses [7, 8] found a positive level of protection against pneumonia, but these estimates might still be a consequence of the inclusion of studies performed in healthier individuals. For HRG, Cornu et al. [8] found a negative and non-significant vaccine protection, in accordance with this analysis. Moore et al. [6] found a higher estimate of VE although the populations they allowed for in their analysis were, exclusively, young healthy adults (Table 2).

VE against IPD

The level of protection against IPD was assessed in six out of the eight studies that were considered in the analysis. Two trials studied the protective effect of the vaccine against IPD in the general elderly population

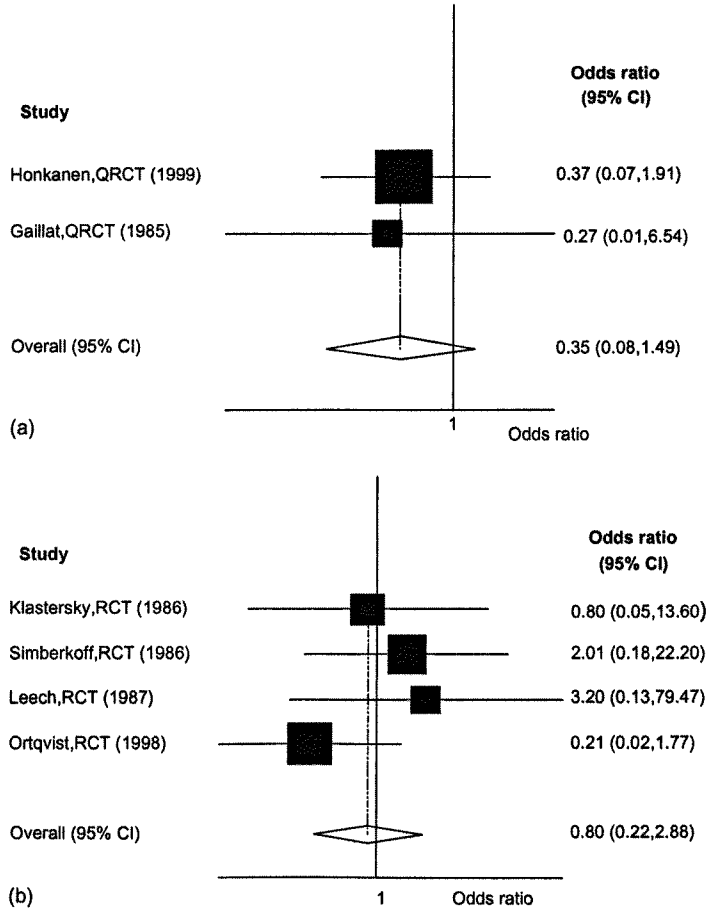

Figure 2. OR (dotted line) and associated 95% CI for IPD in (a) general elderly and (b) high-risk elderly.

[16, 17]. Both of them suggested that the vaccine was protective, though none of them obtained a significant result (Figure 2a). The pooled estimate showed a not significant reduction in the incidence of pneumococcal bacteraemia, VE = 65% (−49–92%).

Four trials were performed among the elderly at a higher risk [18, 20, 22, 23]. The results of these were scattered around a zero effect and all had a lack of statistical power. The pooled estimate of efficacy was weakly positive, VE = 20% (−187–78%) (Figure 2b). A further two trials (both quasi-randomised) were performed on elderly populations which had between 20 and 50% of high-risk individuals [16, 17]. The inclusion of these two trials improved our mean estimate of VE in the high-risk elderly, though this remained non-significant, VE = 44% (−45–79%).

The level of protection against IPD among the general elderly population (65%) was similar to that reported in previous meta-analyses [5–8], i.e. previous estimates ranged between 66% (52–76%) and 82% (66–91%) (Table 2). Previous meta-analyses of VE in HRG also appear to confirm our findings, i.e. estimates of VE are low and non-significant [5, 6]. Fine et al. [5] failed to demonstrate a protective effect against IPD in high-risk elderly, VE = −23% (−449–72%), whereas Moore et al. [6] showed a slightly higher, although non-significant, level of protection against IPD, 47% (−94–86%). The latter included in their analysis three fully randomised clinical trials performed among the elderly with underlying chronic conditions or with a history of community-acquired pneumonia but did not consider the randomised clinical trial that was performed among US veterans in 1987 that did not demonstrate any efficacy, VE = −28% (−153–35%). Cornu et al. [8] found similar estimates of VE to Moore and colleagues when considering a subgroup of patients over 55 years old, VE = 42% (0–82%).

Sensitivity analysis

A sensitivity analysis on the level of protection of the PPV was performed using, initially, a less conservative type of model and then different inclusion criteria with regards to the randomisation process and the study design. Estimates of VE against pneumococcal diseases – which consisted of both pneumococcal pneumonia and IPD cases – in high and low risk elderly were also derived.

For the effect sizes that were produced here, there was no evidence of significant between-study variation, and the two methods produced almost over-

Table 3. Sensitivity analysis of the results

	No. of studies	OR, random effects model (95% CIs)	OR, fixed effects model (95% CIs)	Chi-square (d.f.); *p*-value
All RCT & QRCT				
Pneumococcal pneumonia				
Low risk group (LRG)	3	0.84 (0.47–1.50)	0.96 (0.70–1.30)	5.11(2); 0.078
Mixed risk group (MRG)	6	1.04 (0.68–1.59)	1.09 (0.81–1.46)	7.12(5); 0.212
High risk group (HRG)	4	1.20 (0.75–1.92)	1.19 (0.75–1.89)	2.22(3); 0.527
Invasive pneumococcal disease				
Low risk group (LRG)	2	0.35 (0.08–1.49)	0.34 (0.08–1.48)	0.03(1); 0.857
Mixed risk group (MRG)	6	0.56 (0.21–1.45)	0.54 (0.23–1.30)	3.57(5); 0.613
High risk group (HRG)	4	0.80 (0.22–2.88)	0.73 (0.24–2.20)	2.84(3); 0.418
Only RCT				
Pneumococcal pneumonia				
Low risk group (LRG)	1	0.85 (0.50–1.43)	0.85 (0.50–1.43)	–
Mixed risk group (MRG)	4	1.20 (0.75–1.92)	1.19 (0.75–1.89)	2.22(3); 0.527
Invasive pneumococcal disease				
Low risk group (LRG)	0	n.a.	n.a.	–
Mixed risk group (MRG)	4	0.80 (0.22–2.88)	0.73 (0.24–2.20)	2.84(3); 0.418
Inclusion of Kaufman study [15]				
Pneumococcal pneumonia (LRG)	4	0.58 (0.27–1.26)	0.60 (0.48–0.76)	24.63(3); <0.01
Invasive pneumococcal disease (LRG)	3	0.23 (0.12–0.46)	0.23 (0.12–0.46)	0.39(2); 0.825
Inclusion of Davis study[21]				
Invasive pneumococcal disease (HRG)	5	0.97 (0.29–3.18)	0.88 (0.32–2.43)	3.47(4); 0.483
Inclusion of CCS				
Invasive pneumococcal disease (LRG)	7	0.53 (0.40–0.70)	0.55 (0.45–0.67)	6.57(6); 0.363
Invasive pneumococcal disease (HRG)	6	0.48 (0.29–0.80)	0.50 (0.39–0.65)	5.61(5); 0.346
Two endpoints together				
Low risk group (LRG)	3	0.79 (0.45–1.42)	0.91 (0.67–1.23)	5.19(2); 0.074
High risk group (HRG)	5	1.10 (0.72–1.70)	1.11 (0.72–1.70)	2.78(4); 0.595

RCT = randomised controlled trials; QRCT = quasi-randomised controlled trials; d.f. = degree of freedom; n.a. = not available; CCS = case–control studies.

lapping results (Table 3). If only RCT were considered, the power to detect an effect is significantly reduced as the largest trial used a quasi-randomisation technique [17]. For the general elderly this left only one and zero trials respectively for pneumococcal pneumonia and IPD. For mixed elderly populations, the removal of the QRCT had little impact on estimates of VE, though it further reduced the precision of the results (Table 3).

Although the study by Kaufman et al. appeared methodologically weak, its effect on the pooled estimates was assessed. Including this study in our analysis, results in VE being estimated to be 42% (−26–73%) against pneumococcal pneumonia (i.e. higher but still not significant) and 77% (54–88%) for IPD (i.e. slightly higher with significant 95% CIs). Moreover, the single bacteraemic terminally ill patient reported by Davis and colleagues, was also included in the overall calculation of VE against IPD in HRG, and the final estimate dropped to a very low level with extremely wide confidence intervals 3% (−218–71%). Similarly, the level of protection of the vaccine fell considerably when the two final endpoints were analysed together, VE = 21% (−42–55%) in healthy elderly and a VE = −10% (−70–28%) in high-risk elderly.

VE estimates from case–control and indirect cohort studies [27–33], also including elderly, have generally ranged around 50–80% for IPD (Table 4). Only one study showed no effect when looking at healthy or high-risk adults (30+), and elderly patients (55+) [32]. When looking at the impact that all CCS have on our estimate of VE against IPD, a decrease on the level of protection of PPV is observed in the low risk elderly, VE = 47% (30–60%), whereas a significant and higher estimate of VE is produced in the HRG VE = 52% (20–71%). Indeed, examining the funnel plots, it seems that there may be evidence of bias in studies of high-risk elderly, as the CCS tend to give higher estimates of VE (lower OR) than the RCT.

Discussion

The purpose of this work was to review the published estimates on VE of the PPV and to perform a meta-

Table 4. Case–control and indirect cohort studies of pneumococcal vaccine effectiveness in prevention of invasive disease

Reference	Study type	Setting	Population	Age (years)	Mean age cases (controls)	VE overall	VE in HRG	VE in moderately increased RG	VE in mildly increased RG
Shapiro et al. [27]	Case–control study	Connecticut 1978–1982	Hospitalised patients: 90 cases and 90 controls	18+	62.1 (62.6)	67% (13–87%)	0% (−1228–93%)[a]	77% (27–93%)[b]	70% (1–91%)[c]
Bolan et al. [33]	Indirect cohort method	Canada May 78–Mar 84	Vaccinated invasive pneumo patients: 249; unvaccinated patients: 1638	2+	45 (45)	64% (33–80%)		61% (1–85%)[d]	
Forrester et al. [32]	Case–control study	Denver (US) Sept. 79–Mar. 84	Hospitalised male patients: 89 cases 89 and controls	30+	64.7 (63.9)	−21% (−221–55%)	−67% (−1465–80%)[e]	−23% (−530–71%)[b]	0% (−7743–96%)[c]
Sims et al. [29]	Multicentre case–control study	Pennsylvania Jan. 80–Jul. 86	Hospitalised patients: 122 cases and 244 controls	55+	70.1 (69.2)	70% (37–86%)			
Shapiro et al. [28]	Case–control study	Connecticut, 1984–1990	Hospitalised patients: 1054; hospitalised controls: 1054	18+	67.6 (67.6)	56% (42–67%)	21% (−55–60%)[f]	61% (47–72%)[g]	
Butler et al. [31]	Indirect cohort method	United States, May 78–Apr. 92	Vaccinated invasive pneumo patients: 515; unvaccinated patients: 2322	2+	57 (50)	57% (45–66%)	49% (22–67%)[a]	49% (23–65%)[h]	75% (57–85%)[i]
Farr et al. [30]	Matched case–control study	United States, Jan. 81–Dec. 87	85 cases, 152 controls	2+(~) or 65+		81% (34–94%)			

[a] Including sickle cell anaemia, anatomic asplenia, dysgammaglobulinaemia, haematological, and several other immunocompromising conditions (sickle cell disease, anatomic asplenia, leukaemia, Hodgkin's disease, lymphoma, multiple myeloma, chronic renal failure, nephrotic syndrome, history of organ transplant...). [b] Increased risk of pneumococcal infection: chronic pulmonary disease, alcoholism, diabetes mellitus, renal failure, congestive heart failure, liver disease. [c] 55+ years of age and none of the above conditions. [d] Includes patients (65+) with atherosclerotic cardiovalscular disease, congestive heart failure, COPD, asthma, diabetes mellitus, and no underlying disease. [e] Calculated on patients with immunosuppressive conditions, asplenia, dysglobulinemia, renal transplantation, nephrotic syndrome. [f] Disseminated cancer, lymphoma, splenectomy, multiple myeloma, lupus erythematosus, leukaemia or myelodyspplasia. [g] 55+, chronic alcoholism, congestive heart failure, diabetes mellitus. [h] 5+ years of age with chronic but not immunocompromising illnesses (diabetes mellitus, atherosclerotic coronary vascular disease, congestive heart failure, COPD, asthma, alcoholism, cirrhosis), and those aged 65+ without underlying illness. [i] Patients 65+ years of age; ~2+ and chronic condition OR just 65+.

analysis in order to assess the level of protection among the general elderly population and elderly at a higher risk of infection because of the presence of other diseases. These two groups of individuals are at the centre of the current debate on whether or not to extend the vaccination programme to include all elderly individuals, as has been done in the UK for the influenza vaccine. Randomised and quasi-randomised clinical trials have been taken into consideration and previous meta-analyses have been presented and discussed in order to understand the different results. Due to the small sample size of most of the trials, very wide confidence intervals were estimated for individual studies as well as for the overall pooled estimate.

The results of our meta-analysis when taken with the findings of other meta-analyses and observational studies show that PPV offers a reasonable degree of protection in the general elderly population against invasive disease and a moderate effect in the high-risk elderly. The vaccine appears to have little or no effect against pneumonia.

In the process of selecting the studies and extracting the data, a number of difficulties have arisen, first of which is related to the small number of methodologically strong (Jadad score > 3) studies that satisfied the inclusion criteria and, secondly, their lack of power in detecting any effect of the vaccine. For these reasons, and also because we wanted comparable results with previous meta-analyses, we decided to include all the studies that satisfied our inclusion criteria, whatever their Jadad score was, and to use meta-analysis technique ourselves so that the final estimate of VE would have had more power. Furthermore, as diagnostic methods were not consistent throughout the papers, as well as the separate counting of the number of pneumococcal pneumonia and IPD cases, it was crucial that the two reviewers extrapolated the data separately and then cross-checked them also with previous studies and reviews. The different inclusion criteria adopted for each study population and the definition of high-risk patients which varied across the studies, represent another limitation of the analysis. We tried to take this into account by selecting those studies that were most similar in term of place (all studies are in developed countries), age of the participants and their risk conditions.

Further studies would clearly help clarify whether the vaccine has any effect in these risk groups, and/or on non-invasive pneumonia. It is debateable, however, whether the additional expense of performing these studies would be worth it, particularly as the conjugate vaccine may be effective even in immunocompromised patients. A lack of efficacy against pneumonia does not necessarily preclude the use of the vaccine in the general elderly population. Recent economic evaluations have suggested that the vaccine may be cost-effective in these groups even though its efficacy is limited to invasive disease [34, 35]. Furthermore, it is unlikely that the vaccine would be withdrawn from the currently recommended HRG, even though it may have very little beneficial effect. Bayesian value-of-information analysis [36] is the most logical framework to assess whether more information is required, and if so, how large any trial should be. Meanwhile, trials of the conjugate vaccine should be performed in the elderly.

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Address for correspondence: Alessia Melegaro, Health Protection Agency, Communicable Disease Surveillance Centre, Modelling and Economics Unit, 61 Colindale Avenue, London NW9 5EQ, UK
Phone: +44-20-8200-6868; Fax: +44-20-8200-7868
E-mail: alessia.melegaro@hpa.org.uk

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The 23-valent pneumococcal polysaccharide vaccine. Part II. A cost-effectiveness analysis for invasive disease in the elderly in England and Wales

Alessia Melegaro[1,2] & W. John Edmunds[1,3]

[1]*Modelling and Economics Unit, Health Protection Agency, Communicable Disease Surveillance Centre, London NW9 5EQ;* [2]*Department of Biological Sciences, University of Warwick, Coventry, CV4 7AL;* [3]*Department of Economics, City University, London EC1V 0HB, UK*

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Abstract. The 23-valent pneumococcal polysaccharide vaccine (PPV) has been available for a number of years and is recommended for high-risk categories. Relatively immunocompetent elderly people are not included in this group, although their probability of getting invasive pneumococcal infection is high. The objective of this study was to assess whether vaccinating all elderly people over 65 years of age was a cost-effective policy for England and Wales. The analysis was performed comparing the cost and health effects produced by vaccination, to what would have been occurred if vaccination were not introduced. A decision analysis model was used in order to predict health outcomes under different vaccination scenarios. Unit costs were applied to the outcome and the cost per life-year gained was calculated. Sensitivity analysis was performed to allow for uncertain parameters to vary. The current UK recommendation does not appear to be the most cost-effective strategy due to the low level of efficacy of the vaccine in high-risk groups (HRG) and their shorter life expectancy. Routine vaccination of all elderly appears to be more cost-effective. These results are, nevertheless, very much dependent on the uncertainties around vaccine efficacy estimates, which appear to be still present, especially in HRG, and on the number of hospitalisations and deaths attributable to invasive pneumococcal disease (IPD).

Key words: Cost-effectiveness, Elderly, High-risk, Polysaccharide pneumococcal vaccine

Abbreviations: CDSC/RSIL = Communicable Disease Surveillance Centre's/Respiratory and Systemic Infection Laboratory; CFR = case-fatality ratio; GP = general practitioner; HES = Hospital Episode Statistics; HRG = high-risk group; ICD-10 = International Classification of Disease, tenth revision; ICU = intensive care unit; IPD = invasive pneumococcal disease; LOS = length of stay; MSGP4 = Morbidity Statistics from General Practices; NHRG = non-high risk group; PPV = polysaccharide pneumococcal vaccine; SP = *S. pneumoniae*; VE = vaccine efficacy

Introduction

Streptococcus pneumoniae is one of the most important bacterial respiratory tract infections. It is usually found in the normal flora in the upper respiratory tract and is considered responsible for causing 30–50% of community acquired pneumonia [1, 2], 28–55% of otitis media [3], 20–35% of sinusitis [4], plus a wide variety of other more serious invasive pneumococcal infections such as bacterial meningitis and septicaemia [5].

Invasive pneumococcal diseases (IPD) account for a large number of hospitalisations and deaths each year in Western European countries [6]. In particular, people aged 65+ years are considered at high risk of acquiring an invasive pneumococcal infection and usually experience higher morbidity and mortality rates [7, 8].

The 23-valent-polysaccharide pneumococcal vaccine (PPV) is not currently recommended in the UK for all elderly individuals. The vaccine is licensed for immunisation only to persons over the age of 2 years for whom the risk of contracting pneumococcal pneumonia is unusually high or dangerous [9]. These include persons with asplenia or severe dysfunction of the spleen, chronic renal disease, immunodeficiency, chronic heart, lung, or liver diseases, and diabetes mellitus (in practice most of these are elderly). Although they are recommended to receive the vaccine, uptake rates have been low in this group [10], possibly due to concerns regarding vaccine efficacy and the consequent lack of initiatives for promoting the programme. The recent recommendation in the UK that all elderly individuals (65+) should receive the influenza vaccine provides an opportunity for the introduction of the 23-valent-pneumococcal vaccines

for all the elderly since both vaccines may be given at the same time [6, 11].

Although several economic evaluation analyses have been performed for other European countries [6, 12] as well as for the US [13–18] and generally found that pneumococcal vaccination of the elderly population is relatively cost-effective and potentially cost-saving to the health care sector and to society, no such analysis has been performed for England and Wales at the time of the writing.

This study is thus aiming to assess the costs and the health effects of the introduction of the PPV in England and Wales and to determine whether extending the current UK recommendation to include all elderly individuals, would be a cost-effective programme from the public health perspective.

Methods

Model structure and perspective

A cost-effectiveness analysis was performed to determine the net benefit gained from vaccinating all elderly at 65 years old with the 23-valent polysaccharide vaccines. Hypothetical cohorts – vaccinated and unvaccinated – were followed throughout their lives, and morbidity, mortality and discounted costs of eventual treatment were compared. The perspective adopted was the one of the health care provider (NHS) hence the costs were limited to expenditures and savings within this sector, leaving the costs to society and wider economy out of the analysis. Due to the current recommendation on pneumococcal vaccine in England and Wales [9] and to the differences between elderly with or without underlying risk conditions (in terms of incidence rate, responsiveness to the vaccine, duration of protection and background mortality rate) [19–21], the hypothetical cohorts were each divided into two distinct sub-groups: high-risk group (HRG) and non-high risk group (NHRG). Results for the overall general population were derived within the model, weighting outcomes and costs with the prevalence of high-risk people in the community.

The Morbidity Statistics from General Practices (MSGP4) [22] is a 1-year survey of general practices in England and Wales covering over 500,000 individuals. This survey provided the prevalence and background life expectancy of the two risk groups. Patients were divided according to whether or not they consulted for one of the high-risk codes (based on the current recommendations [9]; Table 1) allowing the proportion of high-risk individuals to be estimated. Background mortality rates were calculated for the two groups and for the general elderly population from deaths recorded in MSGP4. Checks were made to compare the background mortality rate obtained from this survey to those derived from the 1991 Census.

Health outcomes were measured in terms of life-years gained (LYG) from vaccination. The Net Benefit of the program was calculated by multiplying these LYG by their shadow price (which was varied in the analysis) and then subtracting from this the costs of the program. All future benefits and costs were discounted at a constant rate (3% per annum for both in the base case as recommended in the US Panel on Cost-effectiveness [23]). Discount rates were varied in the sensitivity analysis to allow for the UK recommendation levels (6% per annum for costs and 1.5% for health benefits [24]). The model did not take into account population dynamics as herd immunity effects derived from vaccination of the elderly, with a vaccine that does not appear to prevent carriage [25], would be negligible. As the current coverage of the pneumococcal vaccine to the recommended categories remains low [10], the study also assesses the impact of widespread vaccination among high-risk elderly.

Furthermore, health benefits and costs that would derive from widening the current recommendations to include all elderly individuals are taken into consideration as a different scenario. In the base-case the alternative programs were either one-off vaccination at 65 or treatment of IPD as cases occur. Estimates of the optimum age to vaccinate are produced using incremental analysis technique [26], which calculates incremental cost-effectiveness ratios (additional costs that one programme imposes over another divided by the additional benefits, i.e. LYG) for each successive alternative (one-off vaccination at different ages), from the least cost-effective to the most. With the same technique, we looked at the incremental costs and benefits of introducing regular booster doses at specific intervals (5 and 10 years) and assessed what is the optimum interval for revaccination.

Due to the uncertainty that surrounds many of the key parameters included in the model, univariate and multivariate sensitivity analyses were performed. Univariate sensitivity analysis consists of varying one parameter at a time, multivariate sensitivity analysis allows for uncertain parameters to change simultaneously according to the probability distributions that were assigned to them. The model was run 1000 times and on each occasion a random set of input parameter values were chosen by means of Latin Hypercube Sampling using the software @Risk 4.0 (Palisade Corporation, New York). In this way an outcome distribution is produced that gives the proportion of simulations in which the programme is cost-effective (net benefit >0). Uniform, triangular and normal distributions were assumed for input distributions (Table 3).

Epidemiological data sources and vaccine-related parameters

Two data sources were used to estimate the incidence of invasive pneumococcal infections: the HPA Communicable Disease Surveillance Centre's/Respiratory and Systemic Infection Laboratory (CDSC/RSIL) reconciled database and the Hospital Episode Statistics (HES) (http://www.doh.gov.uk/hes). The CDSC/RSIL enhanced surveillance system is based on weekly reports, from public health and non-public health laboratories in England and Wales, of all clinically significant bacterial isolates from blood, cerebrospinal fluid (CSF) and other sterile sites [27]. HES records discharge diagnoses (using the International Classification of Disease tenth revision, ICD-10) of all admissions to National Health Service hospitals in England. It contains non-aggregate data on personal, medical, and administrative details of all patients admitted to and treated in NHS hospital. All records with at least one *S. pneumoniae* related ICD-10 code (G001, A403, J13X, B953) in any of the seven available diagnostic fields were extracted from HES downloads of individual patient data that are available to CDSC. The period considered was April 1995-March 1998. Data were cleaned for possible duplicates and the last episode of each hospitalisation was kept. If more than one pneumococcal code was reported for a single record, the following order of importance was given: Pneumococcal meningitis (G001), pneumococcal septicaemia (A403), pneumococcal pneumonia (J13X), *S. pneumoniae* as the cause of the disease (B953).

A list of high-risk ICD-10 codes was produced based on the current UK recommendations for PPV (Table 1). The presence of at least one of these high-risk codes in any of the remaining diagnostic fields was used to categorise patients at high risk (the remainder being assumed to be non-high risk). Incidence rates were calculated using 1995–1998 HES data and population estimates for England published by the Office of National Statistics and are shown in Table 2. Age-specific incidence rates obtained from CDSC/RSIL laboratory reports of IPD and HES (any *S. pneumoniae* diagnostic code) were very similar (Figure 1). Since it is possible to determine the risk status of patients from the HES database, this data-source was used (rather than CDSC/RSIL) to generate base-case incidence estimates. A uniform distribution was used in the multivariate analysis; lower and upper bounds were set at, respectively, the minimum and maximum values that were observed over the three years period in each age group (based on HES data).

Average lengths of inpatient stay were derived also from HES for the specified age groups. Although clear dissimilarities were not observed between high and low risk patients, specific levels were assigned to the two groups. Minimum and maximum levels that were observed during the analysed period (1995–1998) were used as lower and upper bounds in the multivariate analysis.

Due to the difficulty in determining whether a patient who dies with IPD died of IPD, age and risk specific case-fatality ratios (CFR) for IPD were calculated in two ways. First, all deaths among patients that were admitted to hospital who had a discharge diagnosis including any IPD codes were assumed to have died of IPD (Scenario 1). This gives an upper estimate, as in many instances pneumococcal infection would not be the underlying cause of death as many of these patients also have other codes recorded. A low estimate is produced when considering hospitalised patients that had only IPD codes recorded (Scenario 2). For these, IPD was the only reported clinical condition and, thus, the number of deaths among them was more likely the result of the pneumococcal infection they contracted. Risk-specific CFRs were produced using the proportion of deaths among high-risk individuals that was observed when considering Scenario 1. HES data from April 1995 to March 1998 were analysed and lower and upper bounds were estimated looking at, respectively, the minimum and maximum level observed over the 3 years period for the two scenarios.

ONS 1998 data, reporting pneumococcal disease as the underlying cause of death, were also analysed, although the use of the ninth revision of the inter-

Table 1. ICD-10 codes that were considered in the definition of HRG among hospitalised patients

Code description	ICD-9 code	ICD-10 code
Asplenia or severe dysfunction of the spleen (incl. sickle cell disease and coelic syndrome)	282.5–282.6, 289.4–289.5, 7590	D57; D73; Q89.0
Chronic renal disease or nephrotic syndrome	581, 582, 584, 585	N04; N18
Immunodeficiency or immunosuppression due to disease or treatment, including HIV infection at all stages	0420–0449, 140–208, 279	B20–B24; C00–C97; D80–D89
Chronic heart disease	393–398, 414, 416	I05–I09; I25; I27
Chronic lung disease	490–496	J41–J47
Chronic liver disease including cirrhosis	571–573	K70; K73–K74
Diabetes mellitus	250	E10–E14

Table 2. Base case parameters values and sources

Parameters	Age groups 65–69	70–74	75–79	80–84	85+	Data source
Health outcomes						
Admission rate – HRG[a]	83	126	124	157	250	HES
Admission rate – NHRG[a]	11	17	21	33	82	HES
LOS per admission – HRG (days)	16	15	16	18	18	HES
LOS per admission – NHRG (days)	13	15	16	18	14	HES
High CFR – HRG	16%	18%	21%	24%	28%	HES
High CFR – NHRG	15%	18%	17%	24%	16%	HES
Low CFR – HRG	9%	8%	13%	20%	17%	HES
Low CFR – NHRG	9%	9%	11%	20%	10%	HES
Direct cost[b]						
Cost per GP consultation (£)	19	19	19	19	19	{23}
Cost of initial treatment (£)	8	8	8	8	8	{24}
Cost of inpatient day (£)	242	242	242	242	242	{23}
Cost of intensive care (£)	1103	1103	1103	1103	1103	NHS
Vaccine parameters[b]						
Cost of vaccine & delivery (£)	11.4	11.4	11.4	11.4	11.4	{24}
Vaccine efficacy – HRG (%)	20	20	20	20	20	
Vaccine efficacy – NHRG (%)	65	65	65	65	65	
Duration of protection – HRG (years)	5	5	5	5	5	
Duration of protection – NHRG (years)	6.5	6.5	6.5	6.5	6.5	
Analysis						
Prevalence of HRG (%)	9.6	9.7	10.2	9.7	7.7	{15}
Admitted to ICU (%)[b]	5	5	5	5	5	
Discount rate outcomes (%)[b]	3	3	3	3	3	
Discount rate costs (%)[b]	3	3	3	3	3	
Coverage (%)[b]	60	60	60	60	60	

[a] All rates are per 100,000 populations per year.
[b] These parameters are not age dependent.

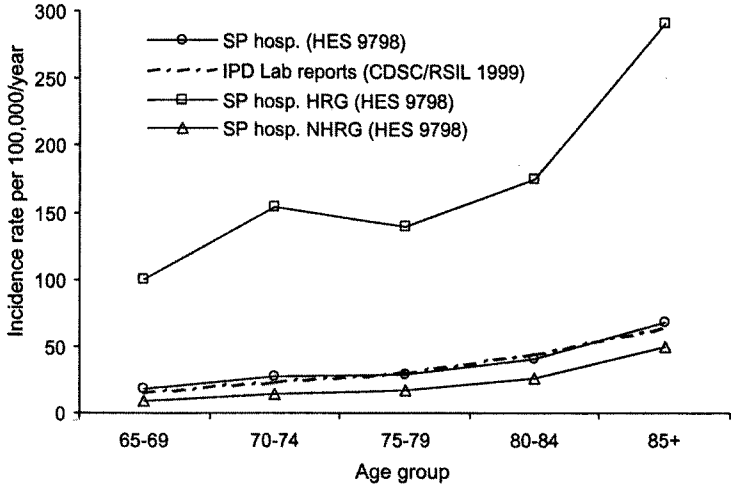

Figure 1. Comparison of admission rates calculated from HES with incidence rates of national laboratory reports of IPD (CDSC 1999). Admission rates are calculated on 1997–1998 data for high and low risk elderly, and for all elderly 65+.

national classification of disease (ICD-9) made it difficult to compare HES figures to the number of deaths reported by ONS. The ICD-9 pneumococcal specific codes are: 0382 for pneumococcal septicaemia, 3201 for pneumococcal meningitis, and 481 for pneumococcal pneumonia. Overall, and due to the inclusion of lobar pneumonia (organism unspecified) in the latter code, the number of deaths reported by ONS was much higher (over 2000 deaths) than that observed in hospitalisation data. Even when looking

at the upper estimate of IPD admissions (Scenario 1 – annual average of 692 deaths).

Vaccine efficacy and duration of protection (vaccine-induced immunity) were assessed reviewing randomised and quasi-randomised clinical trials and case–control studies. As the majority of these studies were insufficiently powered to detect any effect of PPV against IPD, a pooled estimate was performed using a random effect model and having divided the trials in relation to their study population: general elderly population and elderly at high-risk. A detailed description of the procedure used and of the studies that were included for the overall estimate can be found in a separate work [28]. Overall levels of protection of 65% and 20% were used for, respectively, low and high-risk group, although the confidence intervals were very wide. Probability distributions were assigned to vaccine efficacy and duration of protection (Table 3). A range of 5–10 years of protection was found in the literature [29, 30], although some evidence of a lower vaccine-induced immunity was detected in certain high-risk groups [5, 31]. In our analysis, base case values of 6.5 and 5 years for, respectively low and high-risk individuals were adopted. We assumed that adverse events following immunisation would be negligible [32], and have therefore been ignored.

We assumed that each case of IPD would visit the General Practice and receive an antibiotic treatment before hospitalisation. A proportion of the hospitalisations (5%) were admitted in the intensive care unit (ICU) of the hospital. This percentage was varied in the univariate analysis.

Cost estimates

The costs included were the ones of the primary health care (GP consultation and first blind treatment) and the hospitalisation costs. All costs are given in pounds sterling at year 2000 prices.

The unit cost of a typical GP consultation (£19) was taken from the Unit Costs of Health and Social Care [33]. The average initial treatment cost per case was estimated from the standard recommendations given in the BNF for antibacterial therapy [34]. The Formulary recommends erythromycin for the treatment of atypical pneumonia (7 days course, £9.26) whereas erythromycin plus cefuroxime (7 days course, £18.71) for severe community-acquired pneumonia of unknown aetiology. The initial blind therapy for a possible meningitis or septicaemia case was assumed to be respectively a single dose of benzylpenicillin (GP pack = £1.90), or aminoglycoside (£1.51) together with broad-spectrum penicillin (£2.01). The mean cost of the treatment becomes £8.35.

The unit cost per inpatient day was taken from the same standard source [33], using the price of a generic ward (£242) that is the average cost of a variety of specialties. The inpatient cost for the infectious dis-

Table 3. Input distribution for the multivariate analysis

		NHRG		HRG	
Input name	Distribution	Minimum	Maximum	Minimum	Maximum
Admission rate – 65–69 years[a]	Uniform	9.2	13.6	52.1	99.4
Admission rate – 70–74 years[a]	Uniform	14.2	19.4	78.6	153.6
Admission rate – 75–79 years[a]	Uniform	16.4	26.6	73.9	160.1
Admission rate – 80–84 years[a]	Uniform	25.9	40.0	86.3	209.0
Admission rate – 85+ years[a]	Uniform	49.3	112.7	109.4	348.9
CFR – 65–69 years (Scenario 1)	Uniform	13%	17%	15%	17%
CFR – 70–74 years (Scenario 1)	Uniform	14%	22%	15%	18%
CFR – 75–79 years (Scenario 1)	Uniform	15%	19%	20%	23%
CFR – 80–84 years (Scenario 1)	Uniform	22%	26%	17%	26%
CFR – 85+ years (Scenario 1)	Uniform	13%	22%	25%	31%
CFR – 65–69 years (Scenario 2)	Uniform	6%	11%	6%	12%
CFR – 70–74 years (Scenario 2)	Uniform	3%	12%	3%	11%
CFR – 75–79 years (Scenario 2)	Uniform	8%	12%	10%	15%
CFR – 80–84 years (Scenario 2)	Uniform	19%	24%	19%	24%
CFR – 85+ years (Scenario 2)	Uniform	8%	17%	14%	29%
LOS per admission – 65–69 years	Uniform	13.0	13.4	14.5	16.7
LOS per admission – 70–74 years	Uniform	13.6	15.4	14.1	14.8
LOS per admission – 75–79 years	Uniform	15.9	16.1	15.1	16.3
LOS per admission – 80–84 years	Uniform	17.7	18.3	17.0	18.7
LOS per admission – 85+ years	Uniform	12.4	17.3	16.9	19.6
Vaccine efficacy[b]	Normal	−49%	92%	−188%	78%
Duration of protection (years)	Triangular	4	9	3	7

[a] All rates are per 100,000 populations per year.
[b] 95% CIs are displayed.

ease and geriatric wards (£348 and £144) though, were used in the sensitivity analysis as the upper and lower limit. All these costs take into account the average nursing costs, cost of the bed, cost for investigations to ascertain a diagnosis and also treatment costs. The average cost of a bed/day in the ICU was taken from NHS Reference Cost (£1103). Due to a lack of data, we ignored long-term care for sequelae of IPD. Thus cost-estimates are likely to be somewhat higher than is reported here, and our cost-effectiveness estimates will be conservative.

The cost of the vaccine (Pnu-Immune) was taken from the British National Formulary (£9.94), whereas the delivery cost was set at £1.5, similarly to what Ament and colleagues used in their base case analysis (3.00 ecu) [6]. The overall cost of the vaccine for the base-case was thus set at £11.44 and varied in the sensitivity analysis. These unit costs were applied to the estimated outcome predicted by the model.

Results

Life-expectancy

From MSGP4 data, different background life expectancies were estimated for low and high-risk patients, with a probability of survival much lower in the latter case (Figure 2). Almost 10% of individuals over the age of 65 were found to have an underlying high-risk condition. The age specific percentages that were used in the model are reported in Table 2.

Burden of invasive pneumococcal disease

From the base-case analysis, around 3000 invasive pneumococcal infections were estimated annually for England and Wales in 65+ years of age, 34% have a discharge diagnosis indicative of being at high risk. From the MSGP4 survey around 10% of the elderly are high-risk, thus the incidence of IPD is roughly five times higher in HRG compared to NHRG. The overall average length of inpatient stay was estimated to be 11 and 13 inpatient days for non- and high-risk patients, respectively. Age specific figures are shown in Table 2.

If the low estimate is assumed (Scenario 2), an annual average of only around 50 deaths attributable to IPD occurs in the elderly. Taking Scenario 1 gives roughly 500 deaths per year due to IPD.

Cost-effectiveness results

Vaccinating all HR elderly is estimated to have a net discounted cost to the health service of £215,002 (cost of vaccination is estimated to be £302,291 and the discounted medical care savings is £87,289), whereas vaccination of all elderly individuals (65+) is estimated to cost to the health service £2,485,65 (cost of vaccinating the cohort is estimated to be £3,163,165 resulting in discounted medical care savings of £677,510 over their lifetime).

Under Scenario 1 and holding all other parameters at their base case values, the current UK recommendations, which consist of vaccinating all HR elderly with PPV, gives a cost per life year gained of £9477. Vaccinating all 65+ years old, with or without high-risk conditions, results in being the dominating option with a lower cost per life year gained of (£8504) under base-case assumptions. Higher estimates of cost per life year gained are reached when using the lower CFR (Scenario 2): £17,065 and £15,052 for, respectively, HRG and all 65+.

The optimum age at vaccination is determined ranking the different options, from the least costly to the most, and calculating the incremental expenditure

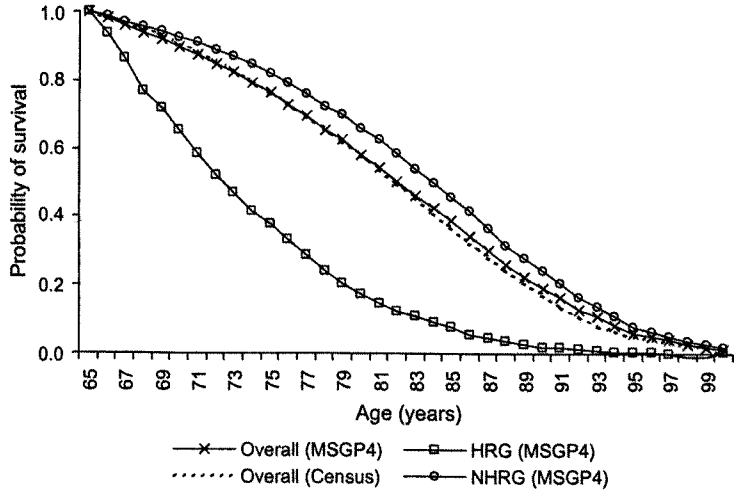

Figure 2. Survival curves for elderly at different risk of infection. Data taken from MSGP4 survey and compared with survival curve published by the Census.

and the additional life years that are gained switching from one option to the following (Table 4). Alternatives that are producing a loss in LYG with an increased expenditure are considered *dominated* options. Assuming a maximum willingness to pay for an extra LYG of approximately £30,000, then the optimum age at vaccination when higher values of CFR are considered is 70 years old for both NHRG and HRG. 75 years appear to be the best option under the low CFR Scenario, although both incremental cost-effectiveness ratios are very close to what could be considered the maximum willingness to pay for an extra LYG. In Table 5 incremental cost-effectiveness ratios are produced comparing one-off vaccination at specific ages (65, 70, 75) to vaccination policies with booster doses every 10 years, and the latter with the option of revaccinating at shorter intervals (5 years). Incremental cost-effectiveness ratios below the level of £17,000 are estimated for both groups of elderly when revaccinating every 10 years and under the high CFR option. This value increases to £26,000 when considering the lower estimates of CFR. Much higher levels of incremental cost-effectiveness ratios are produced when looking at a revaccination policy every 5 years (£23,000–£61,000).

In Table 6 the results of a univariate sensitivity analysis are reported under the two different scenarios. Apart from the CFR, the most influential parameter is estimated incidence of IPD. Basing incidence on the primary discharge diagnosis only results in vaccination being unlikely to be deemed cost effective, regardless of mortality assumptions (£20,000–£54,000 per LYG). It is also apparent from Table 6 that if an extra GP consultation is necessary to vaccinate the elderly (instead of vaccinating opportunistically, presumably with influenza vaccine) then vaccination appears much less cost-effective (range £23,000–£52,000 per LYG). Slightly higher levels of cost per life-year gained (range £10,000–£22,700) are also reached when we assumed that the vaccine was preventing only the additional inpatient days caused by the bacteraemic episode (the average length of stay is from 2 to 3 days longer when looking at IPD compared to other non-invasive pneumococcal disease). Other important parameters include the discount rate: adopting the UK Treasury recommended discount rates means that vaccination becomes slightly more economically attractive than is shown in our base-case analysis (range £8000–£16,800 per LYG).

Figure 3 shows the sensitivity of the results to the different levels of protection of the vaccine in high and low risk elderly. Taking a maximum willingness to pay for a life-year gained of £30,000, for instance, then the model predicts that provided vaccine efficacy is at least 10–15% then vaccination of the high risk would be cost-effective and 25–35% for vaccination of the non-high risk elderly to be cost-effective (holding other parameters at their base-case level).

The results of the multivariate sensitivity analysis, in which all parameters except the discount rate (fixed at 3%) are varied simultaneously, are shown in Figure 4.

The figure shows the probability of each programme being deemed cost-effective (positive net benefit) for different upper limits of society's will-

Table 4. Incremental cost-effectiveness ratios for one-off vaccination policies at different ages

	Low CFR		High CFR	
Age at vaccination	NHRG	HRG	NHRG	HRG
85	£3362	£5418	£2077	£3350
80	£5140	£8493	£7110	£12,102
75	£27,911	£33,202	£11,633	£11,629
70	Dominated	Dominated	£13,168	£4101
65	Dominated	Dominated	Dominated	Dominated

Table 5. Incremental cost-effectiveness ratios – comparisons of different vaccination policies

	NHRG			HRG		
Age at vaccination	65 years	70 years	75 years	65 years	70 years	75 years
Scenario 1 – High CFR						
Vaccination one off	£8422	£6143	£5239	£9477	£7088	£7584
Revaccination every 10 years	£14,602	£11,787	£10,438	£16,746	£13,897	£10,344
Revaccination every 5 years	£37,380	£35,328	£26,309	£29,085	£28,771	£23,680
Scenario 2 – Low CFR						
Vaccination one off	£14,886	£11,048	£7589	£17,065	£13,930	£11,564
Revaccination every 10 years	£21,811	£15,473	£16,892	£25,663	£17,216	£16,714
Revaccination every 5 years	£61,310	£57,120	£32,188	£55,332	£46,459	£28,196

Table 6. Univariate sensitivity analysis. Cost per life-year gained of vaccinating elderly (65+) with PPV

	Scenario 1 (High CFR)			Scenario 2 (Low CFR)		
	NHRG	HRG	ALL	NHRG	HRG	All
Base-case values	£8422	£9477	£8504	£14,886	£17,065	£15,052
Admission rate						
Only first diagnosis admissions	£19,616	£30,000	£20,277	£34,770	£53,999	£35,977
All diagnoses (SP codes + J181)	C.s.	C.s.	C.s.	C.s.	C.s.	C.s.
Intensive care unit						
Proportion to ICU = 20%	£7437	£7744	£7461	£13,144	£13,945	£13,205
Proportion to ICU = 40%	£6123	£5434	£6070	£10,822	£9785	£10,743
Vaccine parameters						
Only protective against invasive part	£10,354	£12,604	£10,528	£18,300	£22,695	£18,635
Protection in HRG = 3, NHRG = 4 years	£12,522	£13,420	£12,596	£22,444	£24,007	£22,572
Protection in HRG = 7, NHRG = 9 years	£6589	£7725	£6674	£11,504	£13,917	£11,679
Costs						
Costs per course of vaccination						
Only vaccine cost (£9.94)	£7031	£7730	£7085	£12,427	£13,919	£12,540
Vaccine cost + GP consultation	£23,782	£28,764	£24,169	£42,034	£51,795	£42,779
Costs per inpatient day						
Infectious disease ward (£348)	£7654	£8126	£7690	£13,528	£14,632	£13,612
Geriatric ward (£144)	£9132	£10,726	£9256	£16,141	£19,313	£16,383
Cost per GP cons & treat						
−25% of the base case	£8426	£9483	£8508	£14,892	£17,075	£15,059
+25% of the base case	£8418	£9471	£8500	£14,879	£17,054	£15,045
Discount rate						
Benefits 6%, costs 6%	£14,786	£13,738	£14,690	£26,449	£24,658	£26,286
Benefits 0%, costs 3%	£5215	£6976	£5333	£9143	£12,568	£9368
Benefits 1.5%, costs 6%	£8264	£9342	£8347	£14,688	£16,808	£14,849

C.s. = cost saving.

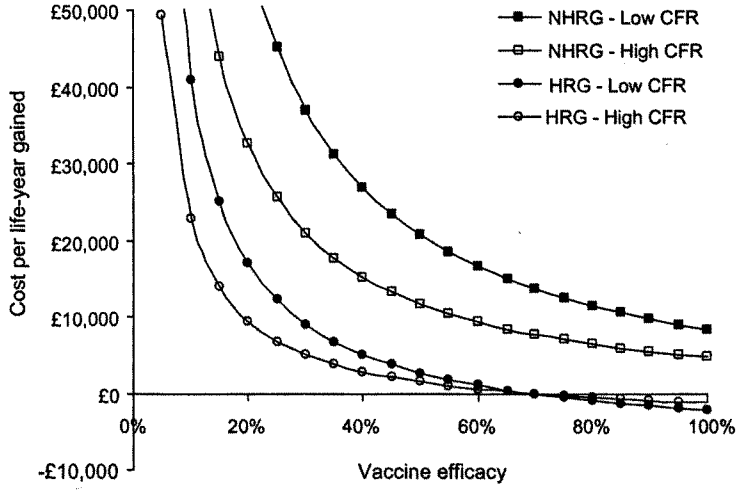

Figure 3. Cost per life-year gained by VE for high and low risk elderly and under the two different assumptions on CFR.

ingness to pay for an additional life-year gained. Vaccination of high-risk groups has a relatively low probability (no more than about 60%) of being cost-effective regardless of which CFR is assumed and regardless of the society's willingness to pay for a life-year gained. This is because the programme has a relatively low probability of being effective. On the other hand, when considering low-risk elderly, a higher proportion of simulations were cost-effective compared to HRG, unless the upper value that society places on a LYG is unrealistically low. The two different scenarios of CFRs are, nevertheless, influencing the rise of the curve and have a strong impact on the probability of having a positive Net Benefit in NHRG when the value of a LYG is around £15,000.

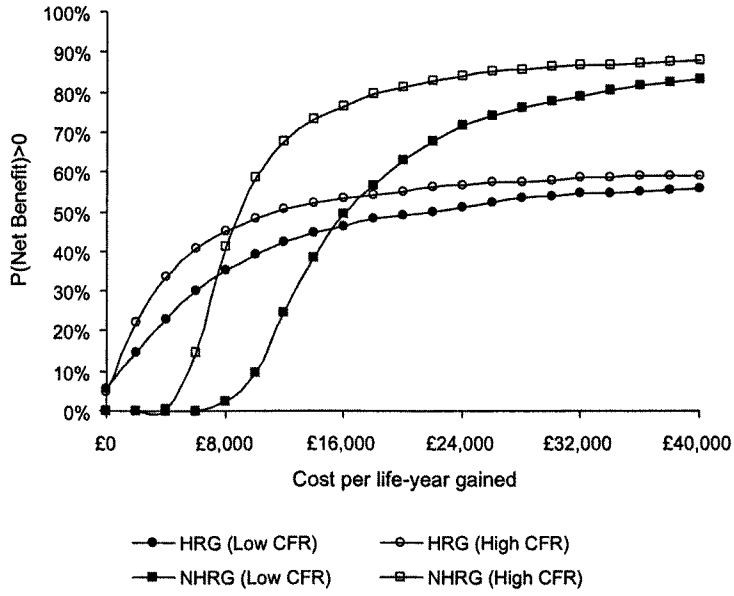

Figure 4. Results of the multivariate analysis. All the parameters are varied within their predefined distribution and the proportion of cost-effective simulations is shown for different values of a life year gained and for high and low risk elderly. CFR estimates are set to the lower or higher values.

Discussion

Invasive pneumococcal disease burden is high among the elderly and, in particular, among those considered to be at high-risk of pneumococcal infection. These are the ones who experience the highest incidence rates, and to whom the vaccine is currently recommended. We presented here an economic evaluation of the current 23-valent-polysaccharide vaccine against IPD, looking at high-risk elderly and at the general elderly population. Although other analyses have been published for other European countries [6, 12] as well as for the US [13–18], this is the first study that considers the UK setting and, in particular, the possibility, which is currently under discussion, of extending the current programme (only high-risk groups) to the general elderly population.

The current UK recommendation does not appear to be the most cost-effective strategy, due to the low level of protection of the vaccine in these risk groups and the shorter life expectancy of elderly patients with chronic diseases. Routine vaccination of all elderly individuals appears to be more cost-effective. Although the relative ranking of these alternatives are unlikely to change, exact quantification of the cost-effectiveness of either of the programmes is hampered by considerable uncertainties in the degree of protection afforded by the vaccine and the number of hospitalisations and deaths that are attributable to IPD. Although many hospitalised patients have IPD and a sizeable proportion of them die, their underlying cause of death was not necessarily IPD, nor could this necessarily be prevented by vaccination. We have attempted to account for some of these problems in estimating the number of preventable life-years being lost by IPD by taking average life expectancy by risk group (rather than for the population as a whole), and by testing the robustness of our findings to very different assumptions regarding CFR. Clearly further work could be performed in this area; the most valid and relevant information would be derived from a properly designed and implemented randomised clinical trial that was appropriately powered to investigate the effect of vaccination on mortality. This is unlikely to happen in the foreseeable future. Therefore, do we have enough information currently available to make a reasonably sound judgement on the cost-effectiveness of vaccination of the elderly with PPV? Provided the vaccine is given opportunistically (at the same time as influenza vaccination, for instance) then it seems likely that vaccination of the non-high risk elderly population would be cost-effective by most criteria, simply because the vaccine is cheap, and the burden of disease is high. Vaccination of high-risk groups does not have a high probability of being deemed cost-effective, because the vaccine may not be effective in these individuals. It seems unlikely, however, that vaccination would be withdrawn from this group.

Moreover, the incremental analysis we performed suggests that the optimal age to vaccinate is 70–75 years depending on whether the, respectively, high or low CFR assumptions are adopted. This produces a lower gain in life expectancy as opposed to vaccinating at earlier ages (i.e. 65 years), but, at the same time, keeps at a lower level the costs associated with the programme. Our analysis also suggests that giving a booster dose of the vaccine every ten years could be

an economically sensible policy to adopt as its additional cost per life-year gained still lies within the acceptable range.

Acknowledgements

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Address for correspondence: Alessia Melegaro, Health Protection Agency, Communicable Disease Surveillance Centre, Modelling and Economics Unit, 61 Colindale Avenue, London NW9 5EQ, UK
Phone: +44-0-20-8200-6868; Fax: +44-0-20-8200-7868
E-mail: alessia.melegaro@hpa.org.uk

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Estimating the transmission parameters of pneumococcal carriage in households

A. MELEGARO[1,2]*, N. J. GAY[1] AND G. F. MEDLEY[2]

[1] *Modelling and Economics Unit, Communicable Disease Surveillance Centre, Health Protection Agency, London NW9 5EQ, UK*
[2] *Department of Biological Sciences, University of Warwick, Coventry CV4 7AL, UK*

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SUMMARY

This paper analyses *Streptococcus pneumoniae* transmission dynamics in households using longitudinal data on pneumococcal (Pnc) carriage in the United Kingdom. Ten consecutive swabs were taken at 4-week intervals from all members of 121 households. The family status is derived from the observed Pnc carriage status of each family member. Transition matrices are built for each family size and composition containing the observed frequency of transitions between family statuses over a 28-day interval. A density-dependent transmission model is fitted to derive maximum-likelihood estimates of the duration of carriage and acquisition rates from the community and from infected individuals within the household. Parameter values are estimated for children (<5 years) and adults (5+ years). The duration of carriage is longer in children <5 years of age than in older family members (51 *vs.* 19 days). Children are 3–4 times more likely than adults to acquire Pnc infection from the community. Transmission rates within the household suggest that adults are more infectious but less susceptible than children. Transmission within the household is most important in large families. The proportion of household-acquired infection ranges from 29 to 46% in households of three persons to 38–50% in larger households. Evidence of density-dependent within-household transmission is found, although the strength of this relationship is not clear from the model estimates.

INTRODUCTION

Background

Streptococcus pneumoniae is one of the most important bacterial pathogens in respiratory tract infections, affecting children and adults worldwide despite current antibiotic therapies [1, 2]. It is responsible for causing upper respiratory infections which may lead to ear infections and sinusitis, as well as more serious invasive disease such as pneumonia, septicaemia and meningitis [3, 4]. Pneumococcus is the leading cause of lobar pneumonia in children under 5 years of age [5].

The bacterium gains entry into the host by colonizing the nasopharynx and the outcome of colonization depends on both the virulence of the colonizing serotype and the efficiency of the host immune system. The interval between colonization and onset of disease, when it occurs, is variable, but there is some evidence that disease is more likely to occur shortly after colonization [6]. However, most of pneumococcal (Pnc) infections remain asymptomatic and *S. pneumoniae* is considered a common component of the nasopharyngeal flora in healthy individuals.

* Author for correspondence: A. Melegaro, Modelling and Economics Unit, Communicable Disease Surveillance Centre, Health Protection Agency, 61 Colindale Avenue, London NW9 5EQ, UK.

Transmission from a person infected with pneumococcus is via droplets of respiratory secretions that remain air-borne over a distance of a few feet. The infecting organism may also be carried on hands contaminated with secretions. As the majority of Pnc-infected individuals remain asymptomatic, carriage data are needed in order to gain an in-depth understanding of Pnc transmission dynamics.

A heptavalent protein–polysaccharide conjugate vaccine has been licensed in the United Kingdom and it is now recommended for children at high risk under the age of 2 years. The vaccine has been proven to be highly effective against invasive Pnc disease [7] and moderately effective against non-invasive Pnc conditions (otitis media, pneumonia) [8–10]. Moreover, some efficacy against Pnc carriage has been shown [11], although there are still concerns about whether serotype replacement will occur if vaccination is widely introduced and what effects this will have on the severity of the disease. Baseline information on the transmission dynamics of Pnc carriage in the pre-vaccination era is thus necessary to predict the effects of interventions such as the introduction of the vaccine on disease burden.

Previous work

Longitudinal carriage studies have been performed to gain insight into the pathogen's mechanism of carriage and transmission within hosts. In this type of study, individuals are swabbed at regular intervals, their carriage status is assessed and inference on their rate of acquisition and on the duration of carriage can be obtained. Smith et al. [12] using longitudinal carriage data collected in Papua New Guinea found that Pnc serotypes vary widely in their acquisition rates and in the length of time for which they persist. An inverse relationship between duration of carriage and age was shown by Ekdahl et al. [13] who studied Pnc carriage using data from an intervention project in Sweden. A similar relationship was found by Auranen et al. [14] who analysed longitudinal data on Pnc carriage in Finnish families taking into consideration transmission within the family and from the community and estimating acquisition rates and duration of carriage for children and adults.

The problem

The aim of this work is to analyse data from a longitudinal carriage study in families in the United Kingdom thereby gaining insights into Pnc transmission dynamics in the pre-vaccination era. In particular, to estimate the duration of carriage for adults and children, and the rate of acquisition of carriage from the community and from infected family members.

METHODS

Description of the data

The dynamics of Pnc transmission within families were captured by a longitudinal study of Pnc carriage conducted in the United Kingdom from October 2001 to July 2002 as part of the European Pneumococcal Project (PncEuro) [15]. The data consisted of follow-up measurements of Pnc carriage of 132 pre-school children (<3 years) and their families, who were enrolled through primary health-care registers in Hertfordshire [15]. The size of the family varied from 2 to 7, although in most of the families there were 3 or 4 members.

From each family member, a nasopharyngeal swab was obtained at initial home visit and followed by 9 further swabs at 4-week intervals. As a previous study [13] suggested that duration of carriage might be less than 28 days, especially in adults, it is possible that not all episodes of carriage will be observed from the data. Although serotyping was performed when Pnc carriage was detected, this analysis considers Pnc carriage in general and, thus, is only looking at whether or not the individual is carrying the bacteria. As there were only three circumstances in which two serotypes were found in the same individual at the same time, the model is based on the assumption that simultaneous carriage of different serotypes is rare enough to ignore initially.

A total of 121 families comprising 489 individuals were considered in this analysis. 11 families dropped out from the study at the very beginning. For each individual that took part in the study, the carriage status at each monthly visit was obtained from the data and then recoded as 0, if non-carrier, 1 if carrier and 9 when either the swab was not taken or the laboratory result not reported. The household state at each visit is derived combining the carriage status of all the family members and results in a sequence of 0s and 1s if their information is complete. Missing information on at least one family member results in incomplete information at the household level

and, thus, a missing value code. Family sequences are organized so that the last number represents the status of the youngest member of the family. Due to the strong association that has been shown in other studies [13, 14] between Pnc carriage and age, with younger children having a much higher prevalence and longer duration of carriage, we set a cut-off at 5 years of age and stratified households by family size and composition (number of adults and children in the family). We derived strings of household results, which were then converted into a table showing the number of transitions between each pair of household states over a 28-day period for each family size and structure. Two households of 2 individuals and one of 7 were excluded from the analysis as their sequences were non-informative. Ten distinct tables $N_{z,u}$ were derived for the available combinations of household size (z) and number of adults (u) respectively in the family: (3, 1), (3, 2), (4, 2), (4, 3), (5, 2), (5, 3), (5, 4), (6, 3), (6, 4), (6, 5). Only complete family transitions, where the infection state of all household members is known on two consecutive observations, are used in the following analysis.

The model

Following the work by Auranen and colleagues on both Hib and Pnc infection [14, 16] the model considers transmission of Pnc within the household. We assumed that each individual can either be in a non-infected state, i.e. susceptible to infection (S), or they can already be infected (carriers) (C) and, as a consequence, able to spread the infection to uninfected individuals in their household. No Pnc-specific disease was observed so this possibility is not included. As in Auranen et al. [14] we set the transition from C→S to be dependent on a constant recovery rate, and the transition from S→C to be a function of the potential exposure to the infective agent both within the family (within-family acquisition rate) and outside the family (community acquisition rate).

The probabilities of transition from an infected to an uninfected state and vice versa in a short time interval δt are then defined for an individual in the age class $i=1, 2$ [where 1 = child (< 5 years) and 2 = adult (5+ years)]:

$$P_i(C\rightarrow S)_{\delta t}=\mu_i\cdot\delta t, \tag{1}$$

$$P_i(S\rightarrow C)_{\delta t}=\left(k_i+\frac{\beta_{i1}I_1(t)+\beta_{i2}I_2(t)}{(z-1)^w}\right)\cdot\delta t, \tag{2}$$

where μ_i and k_i are the clearance and the community acquisition rates respectively for age class i, and z is the family size. $I_1(t)$ and $I_2(t)$ are the number of infected children and infected adults respectively in the family. β_{ij} is the transmission rate from an infected to an uninfected individual and it reflects both the infectiousness of an individual in age class j and the susceptibility of an individual in age class i. Thus the within-household probability of being infected in δt is a function of the number and age class of the other family members that are carrying the bacteria at that particular time. Community acquisition rates and recovery rates are similarly defined in vectors: (k_1, k_2) and (μ_1, μ_2). The term $(z-1)^w$ in eqn (2) represents a density correction factor; $(z-1)$ being the number of other family members in families of size z, and w the factor that controls the extent of density dependence. When $w=0$ the model reflects density-independent transmission: the probability of contracting infection from another specific individual in the family does not change with family size and, thus, the average number of contacts increases linearly with family size. When $w=1$ the probability of getting in contact with the same individual decreases in bigger families although the average number of contacts remain constant. If $w>1$ the average number of contacts decreases with family size. In total nine parameters define the model.

Equations (1) and (2) are used to derive the probability P_{rs} of transition between two different family states r and s in a short time-interval δt. These probabilities are calculated for each household size and composition. It is assumed that in a short time-interval δt, here chosen as 1 day, only one member of the household will change status (either through infection or recovery). The probability of transitions where more than one individual changes status is therefore set to zero. For example, in a family size of three composed of two adults and one child, the probabilities of going from state 001 (two susceptible adults and one carrier child) to states 000, 101 and 011 in one time-step, are derived using respectively eqn (1) to become a fully susceptible household, and eqn (2) to reach states 101 or 011. The $T_1(3, 2)$ matrix [see eqn (3) below], contains all the probabilities of transitions from the initial family status at the top of the matrix to the consecutive status given on the left-hand side

of the matrix when δt is 1 day:

$$
\begin{array}{c|cccccccc}
 & 000 & 100 & 010 & 110 & 001 & 101 & 011 & 111 \\
000 & q_{11} & \mu_2 & \mu_2 & 0 & \mu_1 & 0 & 0 & 0 \\
100 & k_2 & q_{22} & 0 & \mu_2 & 0 & \mu_1 & 0 & 0 \\
010 & k_2 & 0 & q_{33} & \mu_2 & 0 & 0 & \mu_1 & 0 \\
110 & 0 & [2^{-W}\beta_{22}+k_2] & [2^{-W}\beta_{22}+k_2] & q_{44} & 0 & 0 & 0 & \mu_1 \\
001 & k_1 & 0 & 0 & 0 & q_{55} & \mu_2 & \mu_2 & 0 \\
101 & 0 & [2^{-W}\beta_{12}+k_1] & 0 & 0 & [2^{-W}\beta_{21}+k_2] & q_{66} & 0 & \mu_2 \\
011 & 0 & 0 & [2^{-W}\beta_{12}+k_1] & 0 & [2^{-W}\beta_{21}+k_2] & 0 & q_{77} & \mu_2 \\
111 & 0 & 0 & 0 & [2^{1-W}\beta_{12}+k_1] & 0 & [2^{-W}(\beta_{22}+\beta_{21})+k_2] & [2^{-W}(\beta_{22}+\beta_{21})+k_2] & q_{88}
\end{array} \tag{3}
$$

The sensitivity of the model to changes in the definition of δt ($\frac{1}{2}$ day, 2 days) was checked. The daily probability that the family does not change state is given by $q_{rr}=1-\Sigma_{s\neq r}P_{rs}$. Similar formulations of the transition matrix $\mathbf{T}_1$ are expressed for families with 3–6 members and different age structures.

The families transition probabilities for a 28-day interval were then derived as $\mathbf{T}_{28}(3, 2)=\mathbf{T}_1^{28}(3, 2)$. This allowed handling transitions in which more than one individual in the family changes status. Moreover, not having specified the pathway from one state to the next, unobserved events were implicitly included.

Parameter estimation

Maximum-likelihood techniques are adopted to estimate the nine model parameters. The log likelihood $L(z, u)$ and saturated log likelihood $L^*(z, u)$ functions are derived from each monthly transition matrix $\mathbf{T}_{28}(z, u)$ and from the observed number of family transitions between states $n_{rs}(z, u)$. The deviance is then calculated for each family size and composition as follows:

$$\mathrm{Dev}_{z,u}=$$

$$2\cdot(L^*-L)=2\cdot\sum_{r=1}^{2^z}\sum_{s=1}^{2^z}n_{rs}[\ln(n_{rs})-\ln(P_{rs}N_r)], \tag{4}$$

where n_{rs} is the number of family transitions observed in the data from state r to state s and $N_r=\Sigma n_{rs}$. The P_{rs} is the element rs of matrix $\mathbf{T}_{28}(z, u)$ or, in other words, is the model probability that a family of size z and with u adults moves from state r to state s in a 28-day interval. The upper limit of the summations represent the number of family states that are possible for each family size.

The overall deviance [eqn (5)] is obtained as the sum over all family sizes and compositions

$$\mathrm{Dev}=\sum_{z=3}^{6}\sum_{u=1}^{z}\mathrm{Dev}_{z,u}. \tag{5}$$

Maximum-likelihood estimates for the parameters are obtained by minimizing the deviance.

The profile-likelihood method [17] is used to derive confidence intervals for the model parameters. The analysis was conducted using Microsoft Excel.

Model fit

The overall fit of the model could not be formally assessed using a χ^2 test on the residual deviance and degrees of freedom. This was because the expected count for each cell was too small and usually less than 1.

However, after aggregating the states with the same number of carriers, it was possible to assess the goodness of fit visually for each family size by plotting the number of family transitions between states and comparing it to the number obtained from the model after aggregating across cells. χ^2 tests comparing the observed and estimated number of transitions on the aggregated data were performed. Using the χ^2 test in this way only enables the detection of fairly large aberrations in the model fit because the fit is only being tested after the aggregation of data and estimates from a more complex model.

Prevalence of Pnc infection by household size and composition

A steady-state vector $\mathbf{v}$ of dimension 2^z is calculated from any of the family transition matrix [i.e. $\mathbf{T}_1(z, u)$]

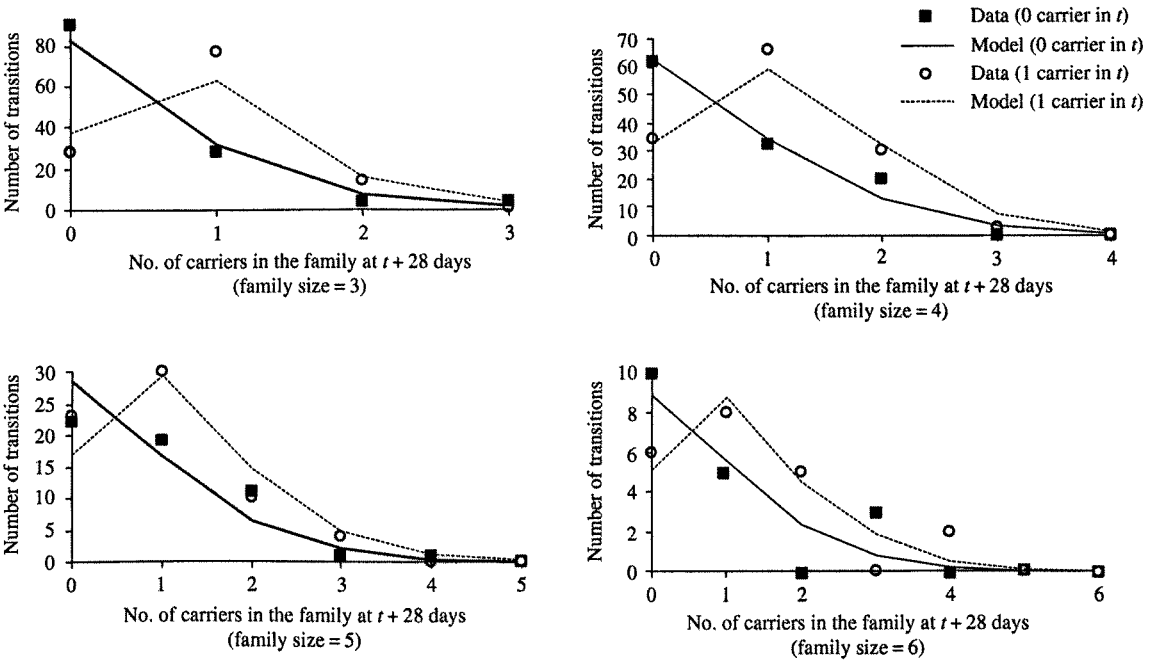

Fig. 1. Transition probabilities obtained from the model for completely susceptible families (——) and families with one carrier (- - - -), compared to proportions of transition observed from carriage data (○, ■).

by solving the following system of equations

$$\mathbf{T}_1(z,u)\cdot\mathbf{v}(z,u)=\mathbf{v}(z,u), \tag{6}$$

where $\mathbf{v}$ gives the proportion of households that are in each specific state at the equilibrium [18]. From this the expected prevalence of infection in children and adults in a household of given size and structure can be calculated.

The proportion of community-acquired Pnc infection is calculated using the steady-state vector $\mathbf{v}$ and deriving the expected number of new infections produced exclusively by household transmission ($k=0$) and comparing it to the expected number of those acquired from the community ($\beta=0$).

RESULTS

We had 560 (51%) complete family transitions in the data (Table 1), the majority of which are found in a family size of 3 and 4. The overall deviance obtained comparing the model log likelihood to the saturated log likelihood is 645, with 180 D.F. (189 non-zero datapoints and nine parameters to estimate). In Figure 1 the fit of the model is shown comparing the expected number of transitions estimated by the model, for uninfected families and families with one carrier, to the number observed from the data for the same transitions. The χ^2 tests of the model fit (not shown) did not show evidence of any significant difference between the model and the data.

Table 1. *Number of complete transitions by family size and number of adults in the family*

Family size	No. of adults 1	2	3	4	5	Total
3	8	226	—	—	—	234
4	—	146	54	—	—	200
5	—	8	27	45		80
6	—	—	14	1	31	46
Total	8	380	95	46	31	560

Estimates of the nine model parameters are shown in Table 2. In children <5 years the mean duration of Pnc carriage, derived using the inverse of the estimated recovery rate, is 51 days (95% CI 42–64). The estimated mean duration of carriage in older family members is close to 19 days (95% CI 14–24). The community acquisition rate for children (0·012 per day) is more than 3 times higher than that for adults (0·004 per day), showing that children <5 years are most likely to introduce the infection into the household. On the other hand, estimates of the within-family acquisition rates show that the highest

Table 2. *Maximum-likelihood parameter estimates*

Description of model parameters	Symbol used	Rates (per day)	95% CI
Community acquisition rate			
Adult	k_2	0·004	0·002–0·005
Child	k_1	0·012	0·008–0·016
Within-family acquisition rate			
Adult to adult	β_{22}	0·048	0·010–0·180
Adult to child	β_{12}	0·106	0·020–0·450
Child to adult	β_{21}	0·005	0·000–0·018
Child to child	β_{11}	0·047	0·008–0·200
Recovery rate			
Adult	μ_2	0·053	0·041–0·070
Child	μ_1	0·020	0·016–0·024
Density factor	w	1·184	0·200–2·200

CI, Confidence interval.

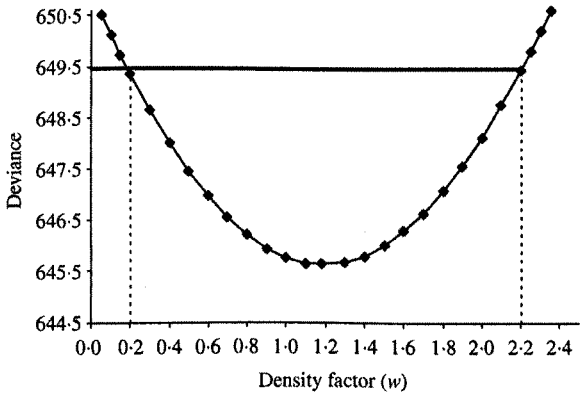

Fig. 2. Profile likelihood for the density factor w (the dotted lines represent the 95% confidence interval).

daily transmission rate is that from adults to children, whereas the lowest is the one from children to adults. These results are consistent with adults being less susceptible to infection. A density coefficient significantly greater than zero ($w=1·2$, 95% CI 0·2–2·2) is estimated from the model and suggests the importance of considering density-dependent transmission. However, due to the very wide confidence interval, no clear indication is given on the strength of this effect (Fig. 2). The sensitivity of the model to variation in the time-interval δt ($\delta t=\frac{1}{2}$ day, $\delta t=2$ days) was assessed and the parameters estimates were found to be not significantly different from the base case results ($\delta t=1$ day).

The expected prevalence of Pnc infection at equilibrium in both adults and children is given in Table 3.

Table 3. *Expected equilibrium prevalence of pneumococcal carriage in household with different compositions (children 0–5 years; adults 5+ years) ($w=1$)*

Prevalence	No. of children in household	No. of adults in household 1	2	3	4	5
Adults	0	0·06	0·10	0·11	0·12	0·12
	1	0·09	0·10	0·11	0·11	0·12
	2	0·10	0·11	0·11	0·11	—
	3	0·10	0·11	0·11	—	—
Children	1	0·44	0·47	0·48	0·49	0·50
	2	0·54	0·53	0·52	0·52	—
	3	0·58	0·56	0·55	—	—

Table 4. *Estimated proportion of pneumococcal infection in adults and children acquired within the family for different household size and composition ($w=1$)*

	No. of children in household	No. of adults in household 1	2	3	4	5
Adult	0	0%	40%	47%	50%	52%
	1	34%	41%	45%	48%	50%
	2	40%	42%	45%	47%	—
	3	42%	43%	45%	—	—
Child	1	22%	29%	33%	36%	38%
	2	46%	43%	43%	43%	—
	3	54%	50%	49%	—	—

In order to have a baseline probability, the expected Pnc carriage in adults is estimated also for families with no children although no such families exist in our data. The prevalence of Pnc carriage in adults does not vary much when bigger families are considered or when more children are present in the family. The expected prevalence in children increases with the number of children in the household. The prevalence increases by 3–10% for each additional child.

The proportion of household-acquired Pnc infection increases in bigger families, reaching 50% for both children and adults (Table 4). When only one child is in the family the proportion in children (22–38%) is lower than in adults (34–50%).

DISCUSSION

Data from a UK Pnc longitudinal carriage study were used and a transmission model fitted using maximum-likelihood techniques to gain some insights into Pnc

transmission dynamics within the household, shedding some light on its mechanism of acquisition and on the duration of carriage. We used these estimates to derive the individual equilibrium prevalence of Pnc infection in households of given size and structure and to assess the importance of household *vs.* community acquisitions.

Although the study was carefully designed and the swabbing interval was forced to its minimum, the presence of unobserved events had to be considered in the setting up of the model. In the past, Bayesian data augmentation methods have been adopted in order to tackle this issue and Markov Chain Monte Carlo (MCMC) simulation has been used to explore the joint posterior of the model parameters and the augmented data [14]. Here we decided to deal with unobserved events by setting up the model for a short time-interval (1 day), during which we assume only one event occurs, and then deriving the probabilities of transitions for longer (i.e. 28 days) intervals. This enabled us to describe the entire data-set with only nine model parameters.

The model classifies individuals as Pnc carrier or non-carrier and it does not consider which serotype they were carrying. Acquisition and clearance rates are thus estimated for carriage of any Pnc serotype. Serotype-specific differences in Pnc acquisition and clearance rates were shown in the past [12] and represent a very critical issue in terms of future disease burden and impact of vaccination policies. Here some baseline information on Pnc transmission dynamics are derived and, although the model allows successive positive tests to be attributed to recovery and reacquisition, it does not exploit the information provided by a change of the serotype carried. Further work will be pursued on these matters.

In agreement with previous findings, the model estimated that children carry Pnc for longer periods than adult family members (51 *vs.* 19 days). Smith et al. [12] estimated approximately 2 months of carriage in children for the most common serotypes (6, 19, 23) and Auranen et al. [14] published an estimate of 2·3 months (95% CI 1·5–3·3), derived for children aged <2 years. The difference between the latter estimate and ours may be due to the younger age group considered. Similarly, the estimated 1·5 months (95% CI 1·0–2·0) duration of carriage derived from the Finnish study [14] in children aged 2+ years is higher than our estimate in the 5+ years group, and this, again, is probably due to their being a younger age group. Moreover, their study allowed for control of exposures but the estimates produced may be imprecise as the study used long intervals between observations (1 month until 6 months of age, and then 3 and 6 months). Slightly lower estimates of the duration of carriage were found in the study of Ekdahl et al. [13], where a clear relationship between carriage and age was observed in individuals with clinical diagnosis of pneumonia and otitis media who were carrying penicillin-resistant Pnc strains. A median of 30 days for children aged <1 year old; 21 days for children 1–2 years; 21 days for children 3–4 years; 12 days for children 5–6 years; 15 days for persons 7–18 years and 14 days for adults 18+ years.

Estimates of Pnc acquisition rates from the community show a difference between children and adults. The former appear 3–4 times more likely to acquire Pnc infection from the community and to introduce the bacteria in their household's environment. Previous work by Auranen et al. [14] showed a similar pattern although the difference between children and adults appears to be stronger in the Finnish data and their rates are significantly lower than ours. Although their model considers only three serotypes that account for 30–60% of infections, this does not fully explain the lower community acquisition rates that they obtain.

The within-family transmission rates incorporate infectiousness of the carrier, susceptibility of the non-carrier and contact between them. Although various individual factors, such as age and immunity levels, may contribute to this relationship, the model used here is from the SIS class, and thus, it does not explicitly account for immunity after infection. Nevertheless, transmission rates within the family were derived considering the age class to which both the carrier and the non-carrier belong (<5 years, 5+ years) and suggested a higher level of susceptibility in children and infectiousness in adults.

The importance of density dependence when looking at transmission dynamics of infection has been discussed previously [19, 20]. We included a density-dependent factor in our analysis and we found it to be an important element of the model and necessary to explain within-family transmission (w significantly greater than 0). However, at this stage, no clear judgement can be made on whether the transmission increases ($w<1$) or decreases ($w>1$) as a consequence of being in bigger families. More work is clearly necessary to investigate this relationship and, thus, to provide better estimates of within-family transmission that takes into consideration changes in the contact

patterns in households of different sizes, environment and composition.

As expected, the prevalence of Pnc carriage for any family size and structure is higher for children than for adults. Moreover, we found that whereas the prevalence in adults does not vary much for different family sizes and composition, the equilibrium prevalence in children increases with the number of children and adults in the family. This may again reflect the lower level of susceptibility in older individuals and, thus, the fact that they are not sensitive to changes in the proportion of infectious contacts they may have within the household.

Household-acquired infection makes a major contribution to Pnc transmission in families both for children and adults. The more siblings that are present in the family the more the infection can circulate among them and persist within the household. However, even in large families approximately 50–60% of children and adults' infections are acquired outside the household.

Longitudinal data can be quite challenging to analyse and many critical aspects have to be taken into account in doing so. Nevertheless they can provide a great contribution to the understanding of a pathogen's dynamics within the human host and on the way individual properties can affect transmission dynamics of the infectious agent. In this paper we tried to draw some conclusions about Pnc transmission dynamics, the contribution of community *vs.* family transmission and the importance of family structure when considering prevalence of Pnc infection within the household. Further analysis is clearly needed in order to provide some specific understanding of serotype-specific Pnc carriage and to be able to give some baseline information on the links between serotypes and transmission in the pre-vaccination era.

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Cost-effectiveness analysis of pneumococcal conjugate vaccination in England and Wales

A. Melegaro[a,b,*], W.J. Edmunds[a,c]

[a] *Modelling and Economics Unit, Health Protection Agency, Communicable Disease Surveillance Centre, 61 Colindale Avenue, London NW9 5EQ, UK*
[b] *Department of Biological Sciences, University of Warwick, Coventry CV4 7AL, UK*
[c] *Department of Economics, City University, London EC1V 0HB, UK*

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Abstract

Aim: To establish whether universal vaccination of infants with the pneumococcal conjugate vaccine is likely to be cost-effective from the perspective of the health care provider (NHS). *Method*: Two hypothetical cohorts – one vaccinated and one unvaccinated – were followed over their lifetime, and the expected net costs and benefits (measured in terms of life-years and quality adjusted life years (QALY) gained) were compared in the two cohorts. The impact of indirect effects of the vaccine, such as herd immunity and serotype replacement, were investigated and their relative importance was assessed by performing univariate sensitivity analysis and multivariate Monte Carlo simulations. *Results*: Under base-case assumptions (no herd immunity and no serotype replacement) the programme is not expected to be cost-effective from the NHS perspective at the current price of the vaccine (assumed £30 per dose, three-dose programme). A reduction of the cost of the vaccine to half of its current level could bring the cost per QALY gained within normally acceptable ranges. If the burden of disease is significantly underestimated by current surveillance systems, then the cost per QALY gained approaches acceptable levels at the current vaccine price. Herd immunity may substantially reduce the burden of pneumococcal disease, particularly of pneumonia among the elderly, leading to a significant improvement in the cost per life year and QALY gained. Serotype replacement would partly offset these benefits, although only with a complete substitution of vaccine types with non-vaccine types and a low level of herd immunity, would pneumococcal vaccination programme would not be cost-effective. *Conclusions*: Conclusions on the cost-effectiveness of pneumococcal conjugate vaccine are sensitive to assumptions regarding the current burden of pneumococcal disease and the future impact that vaccination will have in the unvaccinated and on the future serotype distribution. This study quantifies, for the first time, how these indirect effects may change the cost-effectiveness of pneumococcal vaccination.
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Keywords: Pneumococcal conjugate vaccination; Cost-effectiveness; *S. pneumoniae*; Economics

1. Introduction

S. pneumoniae is a Gram-positive bacterium of the respiratory tract, responsible for a wide range of clinical conditions. In the UK it is one of the major causes of meningitis and acute otitis media (AOM) mainly in children [1], and septicaemia and pneumonia largely among the elderly [2,3]. Although estimating the precise burden of pneumococcal (Pnc) disease and deaths is difficult [4], it is well recognised that Pnc related diseases affect mainly children and the elderly and that severe complications can be associated with pneumococcal infection.

A seven-valent pneumococcal conjugate vaccine (PCV) (Prevenar – Wyeth Pharmaceuticals) was licensed in the UK in 2001 and is currently only recommended to infants aged between 2 months and 2 years who are at special risk [5]. However, evidence of the direct effect of the seven-valent vaccine on the incidence of Pnc disease (invasive pneumococcal disease (IPD), pneumonia and AOM) among healthy

* Corresponding author. Tel.: +44 20 8200 6868.
E-mail address: alessia.melegaro@hpa.org.uk (A. Melegaro).

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children has been shown in a large randomised controlled efficacy study that was conducted by the Northern California Kaiser Permanente [6–8]. A Finnish study [9] estimated the efficacy against AOM. Further studies have shown a reduction in carriage of vaccine serotypes as well as an increase of non-vaccine serotypes among vaccinated individuals [10] and also among their siblings [11]. These results are raising various questions related to the potential long-term effects of the vaccine in the population [12,13], such as will serotype replacement and herd immunity effects occur and, if so, what will be the effects on disease burden? Nevertheless, there is now the need to address questions related to the economic acceptability of the programme with the current knowledge on the vaccine efficacy and on the disease burden.

This study addresses the issue of whether universal infant vaccination with the seven-valent pneumococcal conjugate vaccine (PCV) would be a cost-effective policy under the health care provider perspective (NHS). The analysis takes into consideration the various uncertainties related to the burden of pneumococcal disease and the potential for indirect protection (herd immunity) among unvaccinated individuals as well as serotype replacement effects in the whole population. Different UK vaccination schedules are considered in the analysis as well as the sensitivity of the model results to variations in the vaccine price.

2. Methods

2.1. Cohort model

A model was constructed to follow a vaccinated and an unvaccinated imaginary cohort of individuals from birth until death. The number of life-years (LY) gained from the vaccination programme is taken as the primary measure of the outcome of the programme, and this is compared to its net cost (the net cost being the additional cost of vaccination minus the expected savings from the programme in terms of reduced use of health care resources). Although pneumococcal infection can result in a wide range of outcomes such as invasive disease, pneumonia, ear infections, sinusitis, bronchitis, arthritis, conjunctivitis, peritonitis, etc., the model only considers the four major outcomes for which clinical trial data are available regarding vaccine efficacy: pneumococcal meningitis, pneumococcal bacteraemia, community-acquired pneumonia (CAP) and AOM. Future benefits and costs are discounted according to the current recommendations in the UK [14]: 3.5% per annum for costs and 1.5% per annum for health benefits. Herd immunity, i.e. changes in disease incidence among unvaccinated individuals, is included as part of the scenario analyses as well as changes in carriage and serotype distribution that may be expected to occur after the introduction of pneumococcal vaccination. These two scenarios are further investigated in the multivariate sensitivity analysis.

2.2. Epidemiological data

The epidemiological parameters used in the base-case analysis, are shown in Tables 1 and 2. For the base-case analysis the average annual incidence of both pneumococcal bacteraemia and meningitis was derived extracting the number of invasive pneumococcal disease cases that was reported to the reconciled CDSC/RSIL database [15,16] for the period 1998–2000 and dividing it by the ONS population estimates for England and Wales and for the same time period. Age specific incidence rates were used in the model, using 5-year age bands except in those under 1 year of age, which were grouped in one age category. In the univariate sensitivity analysis the effect of a further age stratification (<6 months, 6–11 months) is explored. CDSC/RSIL is

Table 1
Estimated annual incidence of pneumococcal related diseases, hospitalisations, and GP consultations in England and Wales

Age group	Incidence rate[a]		Hospitalisations rate[b]		GP consultation rate[c]	
	Pnc bacteraemia	Pnc meningitis	Pneumonia with + film	AOM	Pneumonia	AOM
<1	27.3	14.6	221.2	173.2	467	23,636
1–4	10.6	1.6	131.2	203.2	272	24,856
5–9	1.9	0.2	41.7	123.9	62	7,698
10–14	0.7	0.2	17.2	34.3	62	7,698
15–19	1.2	0.1	16.3	13.1	51	2,250
20–24	1.8	0.2	18.1	7.5	51	2,250
25–44	3.1	0.3	26.0	9.1	152	1,741
45–64	6.5	0.5	55.4	11.7	268	1,175
65–74	18.7	0.9	193.6	11.0	508	994
75+	42.5	0.6	697.7	7.5	1161	520
Overall	8.4	0.6	102.7	30.5	266	3,612

All rates are per 100,000 populations per year.

[a] National enhanced surveillance system of IPD cases (CDSC/RSIL).

[b] Hospital Episode Statistics, first diagnostic field (ICD-10 codes for pneumonia: J13, J180, J181, J188, J189; any otitis media codes used for OM hospitalisations).

[c] Royal College of General Practitioners [19].

Table 2
Estimated case fatality ratios and length of stay in the hospital of admitted patients reporting Pnc bacteraemia (ICD-10 code: A403), Pnc meningitis (G001) or pneumonia (codes as in Table 1) in the first diagnostic field

Age group (years)	Case–fatality ratio			Length of stay (days)		
	Pnc septicaemia (%)	Pnc meningitis (%)	Pneumonia (%)	Pnc septicaemia	Pnc meningitis	Pneumonia
<1	4	4	1	5.4	10.5	4.4
1–4	1	4	0	4.6	10.2	2.9
5–9	0	3	1	13.1	9.4	3.2
10–14	0	0	2	6.8	7.2	4.0
15–19	0	11	2	11.0	8.9	4.9
20–24	8	0	3	4.7	12.5	5.0
25–44	20	11	3	12.3	14.3	6.0
45–64	26	18	14	12.7	22.1	9.0
65–74	27	29	29	11.3	20.9	11.8
75+	40	43	46	15.4	25.8	15.4
Overall	22	12	29	11.5	16.9	8.1

currently the most reliable data source on IPD in the UK, as detailed information on the type of specimen (i.e. blood, CSF) is provided together with a clinical description of the patient. The case–fatality ratio (CFR) and the average length of stay (LOS) in the hospital for IPD cases were derived from Hospital Episodes Statistics (HES) [17], using number of deaths and length of stay of all pneumococcal septicaemia (ICD-10 Code: A403) and pneumococcal meningitis (ICD-10 Code: G001) patients, as reported in the first diagnostic field for the period April 1997–March 2000 (Table 2).

The number of hospitalisations for CAP was estimated from HES, extracting all records that were reporting one of the following ICD-10 pneumonia codes in the first diagnostic field over the period April 1995–March 1998:

- Pneumococcal pneumonia: J13 (ICD-9: 481);
- Lobar pneumonia, organism unspecified: J181 (ICD-9: 481);
- Bronchopneumonia, organism unspecified: J180 (ICD-9: 485);
- Other pneumonia, organism unspecified: J188 (ICD-9: 486);
- Pneumonia, organism unspecified: J189 (ICD-9: 486).

Based on a study by Djuretic et al. [18], we assumed that only 79% of these admissions presented with lobar/focal changes and thus had to be considered in order to match as closely as possible the case definition that was used in the Kaiser Permanente trial [7] to estimate the level of vaccine efficacy. Base-case age specific hospitalisation rates were thus derived dividing the number of hospital admissions (first diagnosis) by ONS population estimates for England (Table 1). CFR and the average LOS in hospital for patients with pneumonia were calculated from the extracted data. The annual GP consultation rates for pneumonia were derived from the Royal College of General Practitioners (RCGP) Weekly Returns Service [19], which is a sentinel programme based on a representative sample of the practices (currently around 70) throughout England and Wales. It publishes weekly data on diagnosis (recorded with the ICD-9 coding system), age, and sex of the patient who consults the GP.

Acute otitis media hospitalisation rates were derived from HES extracting any hospitalisation with AOM ICD-10 codes (H650-H678) in the first diagnostic field over the 1999–2000 HES financial year and dividing it by the corresponding ONS population estimates for England. RCGP data were used to derive GP consultation rates for AOM.

2.3. Vaccine efficacy

In the base-case analysis the vaccine was assumed to give no protection against pneumococcal carriage and, thus, no indirect effects such as herd immunity and serotype replacement were considered. This scenario appears to be unrealistic, as some protection against carriage and serotype replacement has been observed. Quantifying the long-term impact of these processes is, however, difficult, hence in the base-case we ignore them. Vaccine efficacy (VE) against pneumococcal disease was based on intention to treat results of recent clinical trials and for IPD this was adjusted to reflect the differing serotype distribution in the UK compared with the population in Northern California at the time of the study [6]. The base-case VE against IPD was therefore 63–87% in the first 5 years of life. VE against all cause clinical pneumonia with a positive film was assumed to be 17.7% (95% CI: 4.8–28.9) [7]; and VE against any confirmed otitis media was 7% (95% CI: −5 to 17%) [9]. Note also that due to the lack of data on serotype distribution of otitis media and pneumonia cases, we do not adjust the VE estimates for these conditions. It is assumed, in the base-case, that children who respond to the vaccine become protected at 4 months of age after three doses of vaccine have been given (accelerated infant schedule). Prior to this age, they are unprotected. In addition, the following alternative schedules were also considered: three doses with the protection starting at 6 months of age (non-accelerated infant schedule); two doses with the protection effective from 6 months of age; and one dose at 1 year of age. Note that in the trials three doses plus a booster were used whereas in

the above schedules 1–3 doses of vaccine are given, and we have assumed that the reduced dosage does not reduce vaccine efficacy. Results of phase 2 trials with pneumococcal conjugate vaccine in UK infants and toddlers demonstrated that two doses of PCV given at 2 and 4 months of age provide satisfactory primary immunogenicity to the serotypes contained in Prevenar [20]. Incremental cost-effectiveness ratios were calculated for each successive alternative, from the least costly to the most, examining the additional costs that one programme imposes over another, compared with the additional benefits it delivers [21]. Clearly, if vaccine efficacy of the different schedules is the same, and protection starts at the same age, then the schedule with the lower number of doses will be preferred. Finally, in the base-case we assume a 10-year period of vaccine-induced protection against disease although in the univariate sensitivity analysis the effect of changes in the duration of protection on the model results were assessed.

2.4. Health outcomes

The primary outcome measure was discounted life-years gained. Pneumococcal specific case fatality ratios were calculated from hospitalisation data (see above). Fatal cases were assumed to lose the average life expectancy for individuals of that age. Life expectancy calculations were derived from current all-cause mortality schedules, derived from ONS tables.

The secondary outcome measure was discounted quality adjusted life-years (QALY) gained which can simultaneously capture gains from reduced morbidity (quality gains) and reduced mortality (quantity gains) and integrates these into a single measure [21]. Reductions in health related quality of life due to pneumococcal disease (calculated on a 0–1 scale where 1 is equivalent to perfect health) were derived from the literature and are summarised in Table 3. A recent study has suggested that the QALY's lost due to acute pneumococcal disease are far greater than the values used here [22]. We have not used these estimates, however, as they are orders of magnitude greater than the other estimates available in the literature. Note that due to the paucity of data we assume that the proportion of IPD patients developing sequelae and the QALY weights attached to these is not age-dependent. This is unlikely to be the case. However, it will only affect the results of the herd immunity scenario (see below), as direct vaccine-induced protection is not assumed to be life-long. As the elderly are more likely to have pre-existing morbid conditions, the QALY loss from the herd-immunity scenario is likely to be overestimated. Other outcome measures include GP consultations avoided, hospitalisations avoided and deaths avoided.

2.5. Costs estimates

The perspective of the study was the health care provider (NHS). Costs to the patient and their carers (i.e. absenteeism, travel to clinics etc) were ignored because of a lack of data on the wider (societal) costs of pneumococcal disease in the UK. Average unit cost estimates of, for instance, an inpatient day and GP consultation, were taken from standard sources and are listed in Table 4. The cost per vaccine dose was set to £30, assuming a volume based discount of approximately £9 (list price of the vaccine is £39.25 per dose [23]). The cost per course of vaccination was calculated multiplying the cost of a vaccine dose by the number of doses and making an additional allowance of £10 per child per dose (nurse consultation cost [24]) for the administration of the schedule. All costs were measured in pounds sterling at 2002 prices (average exchange rate for the time period 2001–2004 £ to US$ and £ to Euro = 1.55 and 1.54, respectively). The average cost of a meningitis case was derived from a case notes review of all meningitis cases <5 years of age from four regions reported to CDSC/RSIL between 1996 and 1999 [25]. This was calculated considering the proportion of patients that experienced different types of sequelae (Table 3) and estimating their related cost using standard sources [24,25]. Similarly, an additional annual cost to the health service was estimated for the subsequent years considering the additional visits and therapies resulting from chronic sequelae of pneumococcal meningitis. Hospitalisation cost for otitis media included the cost of minor ear procedures (most would be tympanostomy) and one ENT outpatient visit. All costs were varied in the sensitivity analysis between ±25% of their base-case values.

Table 3
Outcome from a meningitis episode and QALY lost of pneumococcal diseases

Outcomes from meningitis	% Children [25]
Severe bilateral hearing loss	14
Other sensorineural hearing loss	16
Conductive hearing loss	19
Seizures	16
Outcomes from Pnc diseases	**QALY loss**
Bacteraemia	0.0079 [41][b]
Meningitis	0.0232 [41][b]
Bilateral hearing loss (first year)	0.460 [42][a]
Bilateral hearing loss (subsequent years)	0.200 [42][a]
Other hearing loss (all subsequent years)	0.100 [43][a]
Pneumonia	
Outpatient	0.004 [44][b]
Inpatient	0.006 [41,44][b]
OM	0.005 [45][b]

[a] Per year.
[b] Per episode.

2.6. Sensitivity and scenario analysis

The most likely parameters values were used in the base-case scenario. However, a univariate sensitivity analysis was also performed looking at the effect of changing one parameter at a time within its given range.

Table 4
Unit costs of care and treatment parameters

Parameter	Base value (range)
Cost per vaccine dose	
Cost of vaccine (£)	30 (22–37)
Administration cost (£)	10 (7–12) [24]
Number of doses	3
Cost per inpatient day	
Mean cost of inpatient day (general ward) (£)	273 (205–341) [24]
Mean cost of inpatient day (paediatrics) (£)	398 (298–497) [24]
Mean cost of intensive care bed/day (£)	1232 (924–1540) [46]
Mean cost of paediatric intensive care bed/day (£)	1384 (1038–1730) [46]
Mean length of stay in hospital [17]	
Bacteraemia (days)	11 (variable by age)
Meningitis (days)	17 (variable by age)
Pneumonia (days)	8 (variable by age)
Proportion of bed-days on intensive care (adult) [17]	
Bacteraemia (%)	5 (3.7–6.2)
Meningitis (%)	10 (7.5–12.5)
Pneumonia (%)	1 (0.7–1.2)
Proportion of bed-days on intensive care (child) [17]	
Bacteraemia (%)	3 (2.2–3.7)
Meningitis (%)	6 (4.5–7.5)
Pneumonia (%)	0
Other costs (acute stay)	
Bacteraemia and pneumonia	
X-ray (£)	16 (12–20) [46]
Meningitis	
CT scan (£)	89 (67–112) [46]
Cranial ultra-sound (£)	51 (38–64) [25]
Follow-up (exc. sequelae) (£)	103 (77–129) [46]
MRI (£)	270 (203–338) [46]
Otitis media	
Ear procedures (£)	517 (388–646) [46]
Outpatient ENT consultant visit (£)	52 (39–65) [46]
Proportion undergoing different procedures [25]	
CT scan (adult) (%)	100
CT scan (child) (%)	46
MRI (%)	9
Cranial ultrasound (child) (%)	30
General practice consultation and treatment costs	
Cost per general practice consultation (£)	19 (14–24) [24]
Mean cost of treatment per consultation – IPD (£)	8 (6–10) [23]
Mean cost of treatment per consultation – pneumonia (£)	4 (3–5) [23]
Mean cost of treatment per consultation – OM (£)	2 (1.5–2.5) [23]
Average cost of a meningitis case [25]	
First year (£)	4703 (3528–5880)
Subsequent years (£)	143 (113–189)
Discount rates [14]	
Discount costs (%)	3.5
Discount benefits (%)	1.5

MRI = magnetic resonance imaging.

In addition to the sensitivity analyses and due to the high level of uncertainty that characterise the current and future burden of pneumococcal disease, the following three scenarios were also considered:

(a) *High incidence scenario.* A capture-recapture study [26], estimated the sensitivity of CDSC/RSIL for the diagnosis of pneumococcal meningitis in adults (mean age 55, range 16–97 years) to be 40% (95% CI: 37–44). Incidence rates were thus inflated to take into account possible under ascertainment. For hospitalised pneumonia, incidence rates were inflated by including the following additional codes [ICD-10: J158 (other bacterial pneumonia) and J159 (bacterial pneumonia unspecified)]; any code for pneumonia in any diagnostic field (i.e. not necessarily primary diagnosis); and assuming that all admissions for pneumonia resulted in a positive film (rather than the estimated 79%). For AOM hospitalisations, any AOM codes in any diagnostic fields were considered. An upper estimate of both pneumonia and GP consultation rates was obtained using MSGP4 data [27].

(b) *Inclusion of herd immunity effects.* Whitney et al. [28] recently published estimates of the reduction in IPD incidence in the US in unvaccinated age groups following the introduction of the pneumococcal conjugate vaccine in infants. They estimated the following reduction in IPD incidence among unvaccinated individuals: 32% (95% CI: 23–39%) in the 20–39 years old, 8% (95% CI: 1–15%) in the 40–64 years and 18% (95% CI: 11–24%) in the 65+ roughly 1 year after the introduction of infant vaccination. We allowed for these changes in invasive disease incidence and assumed that a similar indirect effect occurs on the proportion of pneumonia and otitis media cases attributable to a pneumococcal infection (assumed, 48% [3] and 30% [29,30], respectively). The effect of changes in these proportions was considered in both the univariate and multivariate sensitivity analyses. Since the period of protection against carriage appears to be short [31] we assumed that vaccination of one infant cohort will reduce the carriage of pneumococci, and thus the incidence of disease, in other age groups for 1 year.

(c) *Serotype replacement.* Serotype replacement of vaccine types with non-vaccine types has been observed in both pneumococcal carriage [10,32] and disease [9]. The potential effect of a complete substitution of vaccine types with non-vaccine ones on the cost-effectiveness of the programme is explored in this scenario analysis reducing both the direct effect of the vaccine among vaccinated individuals as well as the indirect effect (herd immunity as in scenario (b)) produced among unvaccinated ones [28]. The percentage substitution of vaccine types with non-vaccine types, which in this scenario is set to 100% (i.e. complete substitution), is referred to in the following text as the *serotype replacement coefficient* (SRC). The severity of non-vaccine types in causing IPD is derived from Brueggemenn et al. [33] study, calculating the

non-vaccine versus vaccine types odds ratio (OR) after adjusting by the serotype-specific duration of carriage reported in Smith et al. [34] (OR = 0.16, 95% CI: 0.10–0.25). Non-vaccine serotypes are assumed to be equally severe in causing CAP and AOM (OR = 1).

Note that whereas scenario (a) still maintains the assumption that the vaccine does not produce indirect effects, i.e. no protection against pneumococcal carriage, and simply considers a change in the incidence rates of pneumococcal disease, scenarios (b) and (c) allow the indirect effects of the vaccine at the population level to occur. In particular, scenario (b) considers a reduction in pneumococcal disease among unvaccinated individuals as a consequence of a reduction in carriage. Scenario (c) includes both the herd immunity effect as well as a change in the serotype distribution of pneumococcal carriage, which also produces an effect on pneumococcal disease.

A multivariate sensitivity analysis was also performed using Monte Carlo simulation with @Risk 4.0 (Palisade Corporation, NY, USA) and drawing input parameter values from probability distributions using Latin Hypercube sampling. Uniform distributions were assumed for age-specific incidence rates, case–fatality ratios and length of stay in the hospital as well as for all the parameters related to the cost of care and treatment (Table 4). For incidence estimates the lower limit was set to be the base-case and the upper limit was set to the high incidence scenario (scenario a). CFRs and LOS were varied between ±25% of their base-case values. The SRC was assumed to follow a triangular distribution with a mode of 1, and range of 0–1. A normal distribution was assigned to the log OR estimated from the vaccine trials [6,7,9] and from which the levels of protection were derived (VE = 1 − OR). The proportion of CAP and AOM cases caused by *S. pneumoniae* (48 and 30%, respectively in the base-case) was assumed to follow a binomial distribution with variance determined by the sample sizes of the original studies [3,29]. The herd immunity effect was kept constant at 5% in three out of the five scenarios explored in the multivariate analysis. The other two scenarios considered were the base-case, where no herd immunity and no serotype replacement effect were included, and the Whitney scenario where age-specific indirect protection was assumed to vary within the reported 95% confidence intervals [28]. A distribution of outcome values was generated running the model 1000 times and the results are presented for different levels of herd immunity and under different assumptions on the level of serotype replacement.

3. Results

3.1. Current burden of disease

Table 5 gives the estimated current burden of IPD, all-cause pneumonia and otitis media in England and Wales. There are an estimated 2 million GP visits, almost 76,000 hospital admissions and over 17,000 deaths per year (most of which are attributable to pneumonia in the elderly). The health burden in children less than 15 years of age is large with 46 and 75% of hospital admissions due to, respectively, meningitis and otitis media falling in this age group as well as 62% of GP visits. The estimated cost to the health service related to these outcomes is given in Table 6. In children an estimated 76% of the overall cost is due to treating otitis media.

Table 5
Estimated current burden of IPD, pneumonia (with lobar/focal change) and otitis media in England and Wales[a]

	All ages	Under 15
GP visits	2,083,882	1,346,110
Pneumonia	142,017	14,547
OM	1,941,865	1,331,563
Admissions	75,720	19,989
Bacteraemia	4,407	544
Meningitis	324	148
Pneumonia	54,373	6,904
OM	16,616	12,394
Deaths	17,334	63
Bacteraemia	1,225	11
Meningitis	45	6
Pneumonia	16,064	46

[a] All cause pneumonia and AOM.

From these estimates and assuming that 48 and 30% are the proportions of, respectively, pneumonia and AOM due to *S. pneumoniae* [3,35], the burden of pneumococcal specific disease consists of over 650,000 GP consultations, 36,000 hospital admissions (IPD and non-IPD) and around 9000 deaths in England and Wales per year.

3.2. Base-case results

The estimated reduction in the burden of disease due to the vaccination programme is shown in Table 7. The programme with base-case parameters is estimated to prevent almost 63,000 GP consultations, 1890hospital admissions and

Table 6
Estimated cost (in £) of the current burden of pneumococcal related disease from the health care payer perspective, England and Wales

	All ages	Under 15
GP visits (total)	44,021,605	28,306,271
Pneumonia	3,223,027	330,142
OM	40,798,578	27,976,129
Acute admissions (total)	212,275,776	16,552,586
Bacteraemia	18,645,033	1,424,670
Meningitis	3,873,214	1,415,882
Pneumonia (all cause)	180,303,253	6,660,063
OM (all cause)	9,454,276	7,051,971
Sequelae for meningitis	3,073,240	1,052,566
Total	259,370,621	45,911,423

Table 7
Undiscounted health outcomes and estimated reduction of disease burden in the vaccinated cohort

	No vaccination	With vaccination	Difference
Deaths (total)	19,346	19,331	14
Deaths bacteraemia	1,307	1,301	6
Deaths meningitis	46	42	3
Deaths pneumonia	17,993	17,988	5
Hospital's (total)	77,492	75,602	1,890
Hospital bacteraemia	4,567	4,264	302
Hospital meningitis	318	239	79
Hospital pneumonia	57,527	56,632	894
Hosp OM	15,081	14,467	614
GP consult (total)	1,952,942	1,889,987	62,955
GP consult pneumonia	141,952	140,211	1,741
GP consult OM	1,810,990	1,749,776	61,215

14 deaths, resulting in a total of 1087 undiscounted life-years and 1824 undiscounted QALYs gained in the vaccinated cohort over their life-span (at 1.5% discount rate these are 629 and 1188, respectively).

The base-case programme is estimated to have a net discounted cost to the health service of £71 million, i.e. cost of vaccinating the cohort is estimated to be £75 million (£56 and £19 million for, respectively, administration and vaccine costs) resulting in discounted medical care savings of £4m over their lifetime. The additional cost per life-year gained of vaccination is therefore estimated to be £113,231 under base-case assumptions. The equivalent cost per QALY gained is estimated to be £59,945.

3.3. Sensitivity and scenario analyses

Univariate sensitivity and scenario analyses were performed to assess the sensitivity of the results to changes in the model parameters and assumptions (Table 8). This showed that the most striking changes in the cost per life year or QALY gained occurred when the upper estimates of the incidence of IPD were used as well as when herd immunity effects were included in the model. The vaccine price is also an influential variable. Fig. 1 shows the estimated cost per life-year and QALY gained for different costs of a vaccine dose. At a maximum willingness to pay for a QALY gained of £30,000 [36], the price of the vaccine would have to be reduced to a third of its current value (under base-case assumptions). Under the high-incidence scenario, and with all other parameters at their base-case values, the cost per life year gained drops to £48,257 and cost per QALY gained to £23,800.

The cost per life-year and QALYs gained decreased dramatically if we included indirect protection in older age groups from the introduction of infant vaccination. Using the levels of indirect protection reported by Whitney et al. for IPD and applying them to all relevant outcomes, this indirect effect alone is estimated to result in a reduction of almost 46,000 GP visits, 4800 hospital admissions and 1551 deaths (204 bacteraemia, 6 meningitis, 1341 pneumonias),

Table 8
Cost per LY and QALY gained of pneumococcal conjugate vaccination programme, results from univariate sensitivity analysis

	Cost per LY gained (£)	Cost per QALY gained (£)
Base-case	113,231	59,945
High incidence	48,257	23,800
High IPD incidence	54,066	31,473
High pneumonia incidence	96,960	54,757
High AOM incidence	109,994	41,186
Incidence in <1 year stratified in 0–6 and 6–11 months	111,491	59,482
High case–fatality ratio (CFR)	90,585	52,938
Among IPD cases	96,935	55,046
Among pneumonia hospitalizations	104,661	57,454
Herd immunity[a]	5,297	5,013
Proportion of Pnc pneumonia = 24%	8,597	7,899
Proportion of Pnc AOM = 15%	5,297	5,013
HI effect only on IPD	22,795	18,622
Herd immunity[a] and serotype replacement[b]	30,093	26,683
Vaccine parameters		
Duration of protection (5 years)	123,916	68,169
Duration of protection (15 years)	104,859	54,043
Cost per dose (£20)	83,266	44,081
Cost per dose (£40)	143,197	75,809
Cost of a meningits case		
Increased by 50%	112,523	59,570
Increased by 100%	111,815	59,195
Alternative schedules		
3 doses, protects from 6 months	130,071	66,419
2 doses protects form 6 months	84,335	43,065
1 dose, protects from 1 year	70,699	31,021
Discount rate		
Benefits 3%, costs 3%	174,665	81,594
Benefits 6%, costs 6%	324,847	120,938
Benefits 0%, costs 3%	65,154	38,818
Benefits 1.5%, costs 6%	113,608	60,144

[a] Herd immunity as in Whitney et al. [28].
[b] Complete serotype replacement (100%).

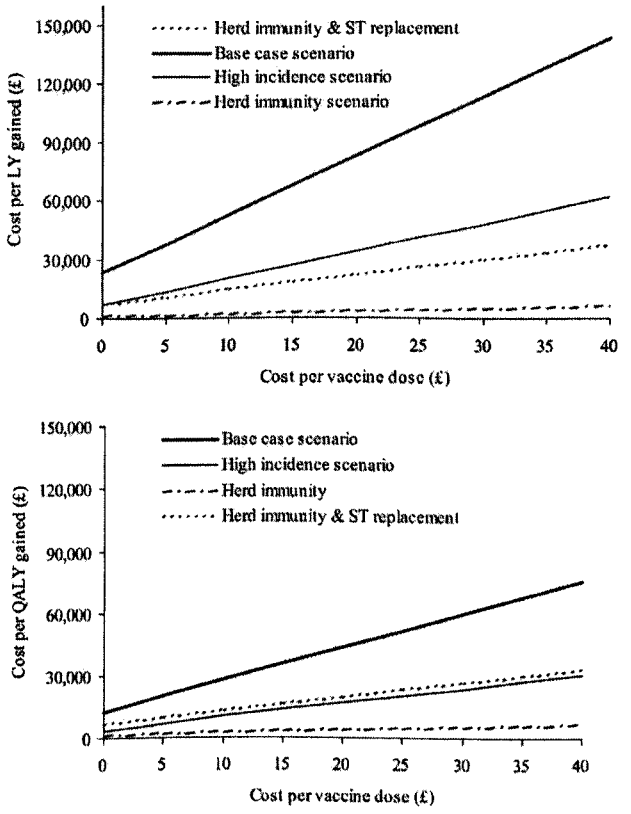

Fig. 1. Sensitivity analysis – cost per life-years gained (top graph) and QALYs gained (bottom graph) for different cost per dose of the vaccine. Herd immunity effect assumed as in Whitney et al. [28]. Complete serotype replacement effect is considered (100%).

the majority of which falls in 65+ years of age (79, 67, 96%, respectively). This generates an additional 12,814 life-years gained (10,319 from pneumonia cases) and 13,017 QALY gained, giving an overall cost per QALY gained of £5013. In case herd immunity effects were only applicable to IPD patients (i.e. different serotype distribution for non-IPD cases), the cost per QALY gained is higher (£18,625) though remaining below what is considered the acceptable range. Moreover, the inclusion of a complete serotype replacement mechanism (i.e. carriage of non-vaccine serotypes completely substitutes carriage of vaccine types) increases substantially the cost per LY and QALY gained though remaining under £30,000. Note that the herd immunity with complete serotype replacement scenario is significantly more cost-effective than the base-case (Table 8, Fig. 4).

3.4. Alternative schedules

Figs. 2 and 3 show the effect of adopting different schedules on the cost per QALY gained of the programme for different levels of, respectively, the cost of the vaccine and the duration of vaccine-induced protection. Note that these results are for the base-case model and neither herd immunity nor serotype replacement mechanisms are included here.

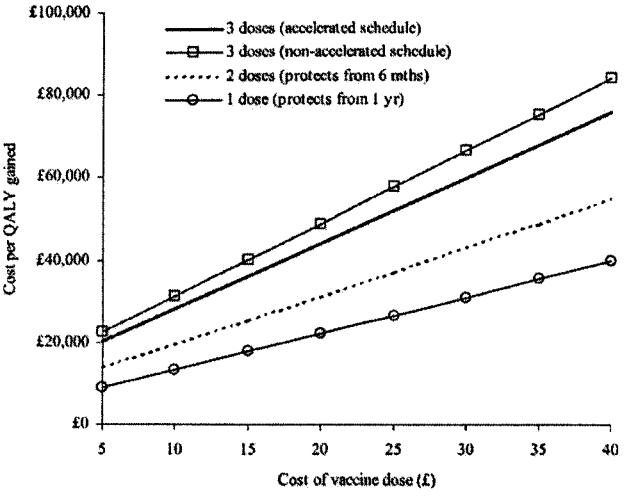

Fig. 2. Cost per QALY gained for different vaccination schedules and varying the cost of the vaccine.

At the base-case cost of the vaccine (£30), a cost per QALY gained in the range of £31,000–66,000 is observed for different vaccination schedules (Fig. 2); the lowest estimate resulting from a one dose schedule at 1 year of age. Although more cost-effective, it should be noted that such a strategy is expected to be less effective than the base-case resulting in 714 discounted QALYs gained in the cohort compared with 1188 in the base-case (Table 9). As expected, three doses and a non-accelerated schedule is the least cost-effective option, having the highest vaccine related costs (three doses) and since vaccine-induced protection is delayed to 6 months of age, after the child has experienced high level of disease rates (30–55 per 100,000 per year in 0–6 months of age, CDSC-RSIL 1996–2000). Results from the incremental analysis are reported in Table 9, where the alternative strategies have been ranked according to their net cost and the incremental cost-effectiveness ratios have been calculated.

We assumed a 10-year vaccine induced protection against disease in our base-case analysis. The cost per QALY gained becomes approximately £79,000 when the duration of protec-

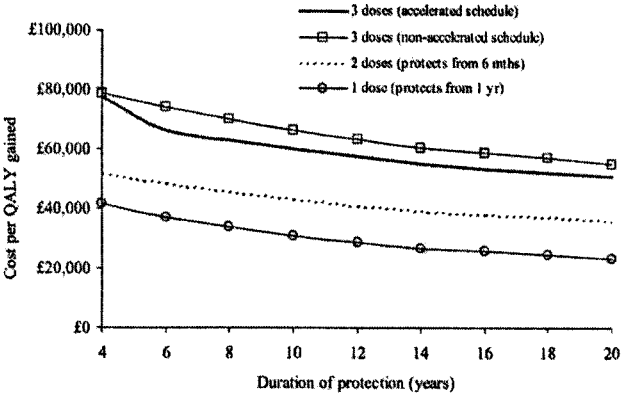

Fig. 3. Cost per QALY gained for different vaccination schedules and varying the duration of vaccine-induced protection.

Table 9
Incremental costs and benefits of alternative strategies, ranked by net cost

Vaccine schedules	Net cost (£)	Incremental cost (£)	Benefit (LY gained)	Benefit (QALY gained)	Incremental benefit (LY)	Incremental benefit (QALY)	Cost:benefit ratio (cost per LY gained)	Cost:benefit ratio (cost per QALY gained)
No vaccination	0	0	0	0	0	0	–	–
1 dose (effect starts at 1 year)[a]	22,141,996	22,141,996	313	714	313	714	£70,699	£31,021
2 doses (effect starts at 6 months)[a]	46,333,060	24,191,064	549	1076	236	362	£102,416	£66,802
3 doses (accelerated schedule)[b]	71,211,084	24,878,024	629	1188	80	112	£312,902	£222,031
3 doses (non accelerated schedule)[c]	71,460,260	249,176	549	1076	−80	−112	Dominated	Dominated

[a] VE assumed to be the same as in the three-dose schedules.
[b] Protection starts at 3 months of age.
[c] Protection starts at 6 months of age.

tion is reduced to 4 years and when three doses are considered in the schedule (Fig. 3). For the one and two doses schedules the cost per QALY gained increases by, respectively, £10,500 and 8400 from their base-case values (£41,585 and 51,466).

3.5. Multivariate sensitivity analysis

In the multivariate analysis (Fig. 4) the impact of different herd immunity and serotype replacement scenarios is explored, keeping the discount rates fixed at their base-case values (3.5 and 1.5%) and allowing the other parameters of the model to change within their specified ranges. In the base-case (no herd immunity and no serotype replacement) 29% of the model simulations resulted in a cost per QALY gained of less than £30,000. When assuming a 5% reduction of Pnc disease incidence among unvaccinated individuals (herd immunity) then 100% of the model simulations are below this level (Fig. 4b, extreme left curve) unless non-vaccine serotypes completely substitute vaccine types (serotype replacement), under which circumstances almost all simulations result in a cost per QALY gained above £30,000. If much higher levels of herd immunity were assumed, such as the ones estimated by Whitney et al. [28], the reduction in disease incidence would be so dramatic that even a complete serotype replacement effect is unlikely to change the cost-effectiveness of the programme (Fig. 4). When a less strong hypothesis is assumed for serotype replacement (i.e. the level of serotype replacement is uncertain and thus is assumed to vary between 0 and 1) and the level of herd immunity is fixed at 5%, then around 90% of the simulations are deemed to be cost-effective at an upper limit of £30,000 per LY/QALY gained. The programme is not cost-effective when looking at the cost per LY gained under base-case assumptions and also when the hypothesis of complete serotype replacement is assumed (in both cases the proportion of simulations that fall above £30,000 is 100%). However, when serotype replacement varies between 0 and 1 or when herd immunity effects are as high as the ones recently published [28], then the cost per LY gained is below £30,000 in, respectively, 85 and 100% of the simulations.

4. Discussion

This paper considers the possible health effects and costs associated with a universal childhood vaccination programme with the pneumococcal conjugate vaccine and establishes baseline information on its cost-effectiveness under the public health perspective. Due to the uncertainties that are related to the current burden of disease and the long-term effects of vaccination on the epidemiology of pneumococcal disease, deriving a precise estimate of the cost-effectiveness of the programme was not possible. However, sensitivity analyses were performed looking at the range within which the cost per life-year gained lies for different prices of a vaccine dose and for different levels of disease incidence rates.

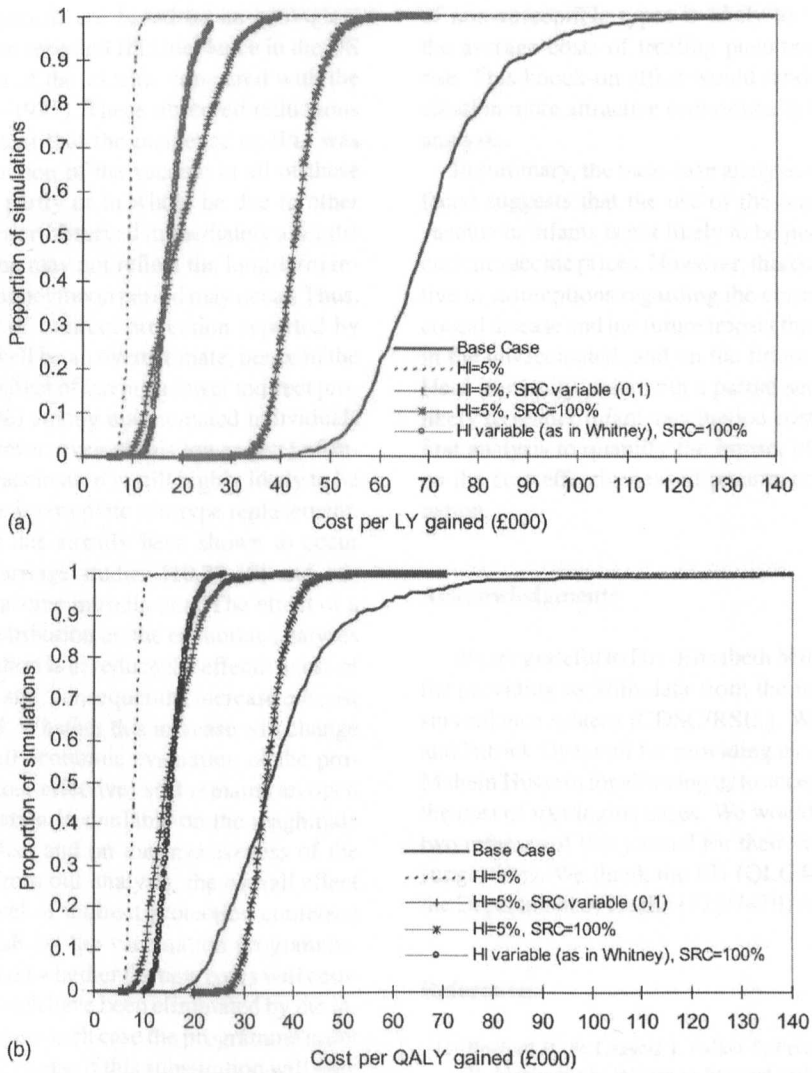

Fig. 4. Cost per LY gained (top graph) and QALY gained (bottom graph) estimated from multivariate sensitivity analysis. Base-case scenario is compared to alternative scenarios that include herd immunity (HI) effect = 5% (- - - -), HI = 5% together with serotype replacement coefficient (SRC) =100% (× × ×), HI = 5% and SRC that varies between 0 and 100% (+++), HI as in Whitney and SRC = 100% (circles).

In addition, to take into account the impact of pneumococcal vaccine not only in terms of life-years saved but also considering the effect of morbidity on survivors, the cost per QALY gained was also estimated. The possible impacts of herd immunity and serotype replacement were investigated as scenario analyses and in the multivariate sensitivity analysis.

Ignoring potential herd-immunity effects, universal vaccination of children with the pneumococcal conjugate vaccine is not likely to be deemed cost-effective from the NHS perspective at the current price of the vaccine. The latter should be set at around £10–15 per dose in order to get a cost per QALY gained of approximately £30,000. On the other hand, if the current burden of pneumococcal diseases was greatly under estimated by the national surveillance systems, then the cost per QALY gained, at a £30 cost per vaccine dose, could reach acceptable values.

A two-dose non-accelerated programme is estimated to be more cost-effective than a three dose accelerated programme, assuming both result in similar vaccine efficacy. Nevertheless, at the current price of the vaccine, this is still not within the generally accepted threshold unless herd immunity effects occur without significant serotype replacement. Further work will clearly be needed when the results of the UK vaccine trials become available.

From the univariate sensitivity analysis the model estimates that the infant vaccination is highly likely to be cost-effective if the levels of indirect protection observed by Whitney et al. [28] are attributable to the vaccine and apply equally for each subsequent vaccinated cohort. Rates of pneumococcal disease are very high in the elderly and the consequent reduction of the number of cases in these age groups, without additional costs, has a large effect on the overall cost-effectiveness of the programme. It should be stressed,

however, that these reductions are based on an ecological analysis of the reduction in reported IPD incidence in the US just after the introduction of the vaccine compared with the period just before (1998–1999). These observed reductions should be set in the context that the incidence of IPD was falling before the introduction of the vaccine in all of these age groups, and so may partly or in whole be due to other factors. Finally, the reduction observed immediately after the introduction of the vaccine may not reflect the long-term reduction in incidence as a honeymoon period may occur. Thus, taken together, the level of indirect protection reported by Whitney et al. [28] may well be an overestimate, hence in the multivariate analysis the effect of having a lower indirect protection of the vaccine (5%) among unvaccinated individuals is also investigated. However, even at this lower level of indirect protection, infant vaccination is still highly likely to be cost-effective unless there is complete serotype replacement.

Serotype replacement has already been shown to occur in both pneumococcal carriage studies [10,37,38] and otitis media [9] following vaccine introduction. The effect of a change in the serotype distribution on the economic analyses of pneumococcal vaccination is to reduce the effectiveness of the programme over time and, consequently, increase the cost per LY and QALY gained. Whether this increase will change conclusions on the overall economic evaluation of the programme (making it not cost-effective) still remains an open question, as little information is available on the magnitude of the herd immunity effect and on the invasiveness of the non-vaccine serotypes. From our analysis, the overall effect depends firstly on the level of indirect protection conferred to unvaccinated individuals by the vaccination programme. Moreover, it also depends on whether the new types will completely substitute those which have been eliminated by the introduction of the vaccine (in which case the programme is not likely to be cost-effective) or else if this substitution will only be partial and, in other words, carriage of pneumococci (any serotype) will be reduced as a consequence of the introduction of the vaccine. In this latter case, although serotype replacement would increase the cost per LY/QALY gained in respect to the situation in which only herd effects were present, infant vaccination would be deemed cost-effective under most circumstances. Our conclusions on serotype replacement rely heavily on a two-strain model by Lipstich [39,40] that shows that carriage of the non-vaccine type increases up to the level (but not beyond) that of the original vaccine-type. However, it should be noted that Lipsitch also suggests that with more than two strains it is possible to increase the prevalence of carriage over the pre-vaccination level. We did not look at this possibility in our analysis and, therefore, our estimates of the negative effect of serotype replacement may be somewhat underestimated.

Currently a higher proportion of vaccine types have decreased susceptibility to antibiotics than non-vaccine types. Hence widespread immunisation should lead to a reduction in the circulation of resistant organisms (at least in the short term). If current trends continue, then the future prevalence of non-susceptible types is likely to increase and therefore the average costs of treating pneumococcal cases will also rise. This knock-on effect would render pneumococcal vaccination more attractive economically than is apparent in our analysis.

In summary, the base-case analysis (excluding indirect effects) suggests that the use of the pneumococcal conjugate vaccine in infants is not likely to be justified economically at current vaccine prices. However, this conclusion is very sensitive to assumptions regarding the current burden of pneumococcal disease and the future impact that vaccination will have in the unvaccinated, and on the future serotype distribution. Herd immunity, even with a partial serotype replacement, is likely to render infant vaccination cost-effective. This is the first analysis to quantify the impact of these indirect effects on the cost-effectiveness of pneumococcal conjugate vaccination.

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